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CHAPTER 28

Cardiovascular adjustments to gravitational stress

C. GUNNAR BLOMQVIST

Departments of Internal Medicine (Cardiology) and Physiology,
Weinberger Laboratory for Cardiopulmonary Research,
Southwestern Medical School, University of Texas
Health Science Center, Dallas, Texas

H. LOWELL STONE

Department of Physiology and Biophysics, University of
Oklahoma Health Science Center, Oklahoma City, Oklahoma

CHAPTER CONTENTS

THE EFFECTS OF GRAVITY on the cardiovascular system must be taken into account whenever a hemodynamic assessment is made. All intravascular pressures have a gravity-dependent hydrostatic component. The interaction between the gravitational field, the position of the body, and the functional characteristics of the blood vessels determines the distribution of intravascular volume. In turn this distribution largely determines cardiac pump function.

Multiple control mechanisms are activated to preserve optimal tissue perfusion when the magnitude of the gravitational field or its direction relative to the body changes. Humans are particularly sensitive to such changes because of the combination of their normally erect posture and the large body mass and blood volume below the level of the heart. Current aerospace technology also exposes human subjects to extreme variations in the gravitational forces that range from zero during space travel to as much as nine-times normal during operation of high-performance military aircraft. This chapter therefore emphasizes human physiology.

HYDROSTATIC PRESSURE

Models

Hydrostatic pressure is a force acting in a fluid system as a result of a gravitational field. The hydrostatic pressure is a static pressure in both open and closed fluid systems and is added to other forces generated in the system. In the cardiovascular system

the action of the heart generates a dynamic pressure. The elastic properties and the pressure-volume characteristics of the peripheral vascular compartment modify both the dynamic and the static pressure components.

The various pressure components and their interactions are considered in a series of models of increasing complexity, starting with a simple, rigid, open cylinder. Such a cylinder of height h, filled with fluid of density ρ, has forces acting in various directions unless the fluid is completely at rest. At rest the major force acting on the fluid is a static pressure force generated by the gravitational field and directed perpendicularly to the earth's surface. The difference between the pressure at h and that at the surface of the fluid is directly proportional to h. This result can be derived by considering the balance of forces acting on some horizontal plane in the fluid (55). This force at rest is strictly vertical, implying that the horizontal components of the pressure force balance. The vertical pressure is therefore independent of the horizontal position in the cylinder. The weight of an element in the fluid at h must be balanced by an upward pressure force at the bottom of the plane. This force is greater than the downward pressure force at the top. If A is the cross-sectional area of the horizontal plane and if P_1 and P_2 are the pressures acting on the bottom and top, respectively (Fig. 1), then the net upward force on the horizontal plane is $(P_1 - P_2)A$. This pressure force equals the downward-acting weight of the fluid above the horizontal plane. The downward-acting force of the fluid equals the product of ρ, the volume (Ah'), and the force of gravity (g). Thus

$$(P_1 - P_2)A = \rho g A h'$$
$$P_1 - P_2 = \rho g h' \tag{1}$$

If P_2 is atmospheric (P_A), the surface of the tank is at $h = 0$, and in the fluid h is negative, the pressure anywhere in the tank (P) is

$$P = P_A - \rho g h \tag{2}$$

As the depth below the surface of the tank increases, the pressure force increases. The pressure in Equation 2 is the hydrostatic pressure for a fluid at rest in a rigid tank (55).

When the same cylinder is closed rigidly at both ends and filled with fluid until all air is excluded, the pressure at the top of the cylinder is negative and approximately one-half of the pressure in the cylinder shown in Figure 1A. The pressure at the bottom is equally large but of the opposite sign (Fig. 1B) and P = 0 at 0.5 h. The elastic properties of the circulatory system are disregarded by this model. Replacing both rigid ends of the closed cylinder with elastic membranes of identical properties results in a set of circumstances similar to those in the rigid, closed model (Fig. 1C). When one end of the cylinder is closed with an elastic material more rigid than that at the opposite end, however, the point in the fluid at which the
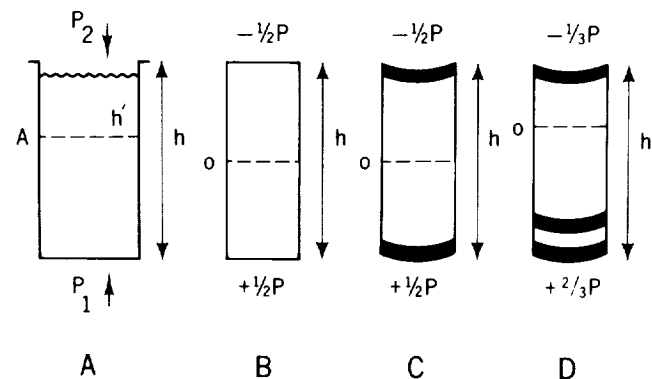

FIG. 1. Hydrostatic pressures (P) in simple fluid-filled systems of height h. Relationship of hydrostatic pressure and zero in cylinder open to atmosphere (*A*) and cylinders closed at both ends with rigid membranes (*B*), with membranes of equal elasticity at both ends (*C*), and with membrane more elastic at upper end (*D*).

hydrostatic pressure is zero moves toward the less rigid end. The magnitude of the shift in the zero point depends on the elastic properties of the ends of the cylinder (62). Including a pump in the system (e.g., heart in circulatory tree) does not change the location of the zero hydrostatic pressure point in the system but adds an additional pressure component (dynamic pressure). Thus the pressure at the top of the cylinder in Figure 1D equals the sum of $-\frac{1}{3}$ P and the pressure generated by the pump.

When the cylinder is closed at both ends (Fig. 1C, D), the hydrostatic pressure at the bottom differs from that expected in an open-ended cylinder. The pressure difference between the top and the bottom corresponds to the full effective hydrostatic pressure of the open system given in Figure 1A, but part of the column in the closed system in Figure 1C is suspended from the top of the cylinder and exerts a negative pressure there. Only a portion of the total pressure difference between top and bottom is positive at the bottom of the cylinder.

In summary, three components contribute to a pressure measured anywhere within a closed fluid system, e.g., the cardiovascular system. The first component is the hydrostatic pressure, which in a stable body position is static. The complex second component reflects overall and regional elastic properties of the blood vessels, particularly the pressure-volume relationships of the veins. In general it is a static pressure but changes when the characteristics of the system are altered. The third component is the dynamic pressure that the heart generates.

Hydrostatic Indifference Point

One would assume from these considerations that during postural changes intravascular pressures in dependent regions would rise, intravascular pressures in superior regions would fall, and pressure at some intermediate point would remain constant. Pressure measurements have been made in dead and in anesthetized animals during changes from the horizontal

to the head-up and head-down positions (61, 83, 135, 225, 308). Clark et al. (61) measured intravenous pressure at several sites in dead animals. When the animals were tilted from the horizontal position either head up or head down, the equilibrium pressure equaled the sum of the hydrostatic pressure generated by the new position and the static pressure measured in the horizontal position. When the catheter tip was ~6 cm below the heart, the hydrostatic pressure was independent of body position. This point has been referred to as the hydrostatic indifference point (HIP) for the measurement of venous pressure. Anesthetized dogs produced similar results, but the HIP was 12 cm below the heart. This implies that the autonomic nervous system and changes in venous tone can influence the anatomical location of the HIP. In either case head-up tilt decreased and head-down tilt increased intracardiac pressures. However, changing the position of the HIP changes the magnitude of the pressure change at any intravascular site as a result of postural change. Guyton and Greganti (135) repeated the studies of Clark et al. (61). They placed a catheter in the right atrium and then changed the position of the tip until changes in body position produced no changes in pressure. The apparatus they used allowed them to define the position of the HIP relative to the three major axes of the body. The HIP was located within the right ventricle (Fig. 2) immediately below the level of the tricuspid valve. Interventions like reduction of blood volume, epinephrine infusion, and destruction of the spinal cord did not alter the anatomic location of the HIP for venous pressures but affected the position of the HIP for the arterial system (308). Guyton and Greganti (135) postulated that the venous HIP was located within the heart to maintain stable ventricular filling pressure and cardiac output during changes in body position. Stroke volume, however, decreases by about 30% in humans tilted from the horizontal to the head-up position (224, 260, 345) mainly because of changes in ventricular filling pressures. Thus a species difference in the response to postural changes exists. Direct measurements suggest that the anatomical location of the HIP in humans is outside the heart. Gauer and Thron (110) defined, by measurements in the horizontal position and during

head-up tilt, a venous HIP site a few centimeters below the diaphragm. Progressive head-down tilt initially caused the expected increase in cardiac filling pressures, but later it caused a paradoxical fall, implying a shift in HIP from a position below the heart to a position above the atria.

Factors such as the compliance, volume, and size of the components of the venous system determine the anatomical position of the HIP. Any change from basal conditions that affects one or more of these factors is likely to alter the position of the HIP. The pressure-volume curves of isolated veins are nonlinear and shift in response to physiological stimuli (109, 118, 185), whereas the effective systemic vascular pressure-volume relationship (as defined by volume infusion and withdrawal in intact subjects) approaches linearity (80). The pressure-volume characteristics, either through a pure volume change or through a change in the characteristics of the vessel wall (compliance), may change to a different extent in different regions. The position of the HIP theoretically should shift away from the region with a decrease in compliance. However, Guyton and Greganti (135) found that neither hemorrhagic volume depletion nor denervation by spinal ablation affected the position of the HIP in anesthetized dogs. The results are difficult to explain unless there were offsetting compliance changes caused by a combination of alterations in volume and in neural and myogenic control.

Transmural Pressure and Tissue Filtration

The three components of the pressure measured anywhere in the vascular system may be restated as *1)* the hydrostatic pressure caused by the force of gravity, *2)* the static filling pressure of the resting circulation (61, 134, 140), and *3)* the dynamic pressure from the relationship between blood flow and resistance (229). The properties of the tissues surrounding the blood vessels and their effects on the relationship between intravascular and transmural pressures in the various portions of the vascular system should also be considered. This particularly applies to the low-pressure portions of the vascular system. The transmural pressure (P_T) is

$$P_T = P_i - P_e \qquad (3)$$

where P_i is the intravascular pressure and P_e is the extravascular pressure. In *Hydrostatic Indifference Point*, p. 1026, the change in intravascular pressure with changes in body position is discussed in reference to the HIP. The effect of the gravitational field on the pressure forces outside of the vascular compartment, however, must also be taken into account. Changes in these forces may dramatically alter the effect of changes in the intravascular hydrostatic pressure component.

The tissues surrounding most of the blood vessels in the mammal are composed of 70% water, which has a specific gravity of 1. Because the outer covering of

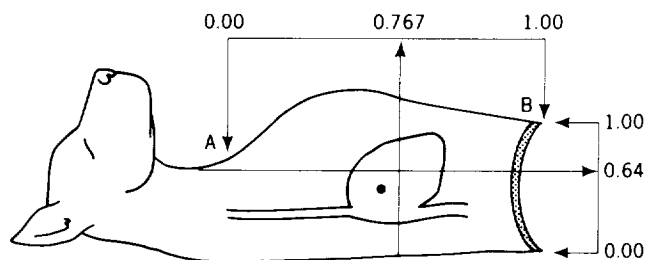FIG. 2. Hydrostatic indifference point (HIP) in anesthetized dog is in right ventricle. *A*: sternal notch; *B*: xiphoid process. Distance between reference points is 1.00; coordinates of HIP are fractions. [Adapted from Guyton and Greganti (135).]

the body has elastic properties, it may serve as a pressure garment under many conditions. In addition many of the blood vessels pass through cavities that do not connect directly with the outside environment. Because the body is mostly water, these cavities may be expected to behave like fluid-filled systems. Changes in body position within a gravitational field would be expected to alter the pressure in these tissues in direct proportion to the vertical height of the fluid columns. From Equation 2 the expected gradient in hydrostatic pressure composed mostly of water equals 1 cmH_2O/cm of vertical height above or below the reference level.

Extravascular pressure changes with varying body position have been measured in the cerebrospinal fluid compartment (139, 216, 217) and the abdominal cavity (284). The extravascular pressure in these systems also changes with gravitational force and modifies the effective vascular pressure, i.e., the transmural pressure. In the cerebrospinal fluid system the HIP in normal subjects is located between C_7 and T_5 in the spinal

column. This location, which is similar to that of the venous HIP, tends to minimize postural changes in effective transmural vascular pressures within the central nervous system. Pressure has been measured in the pleural and pericardial cavities in conjunction with simultaneous measurements of vascular pressures in experimental animals (9-11, 68). The intravascular pressures in the right and left atrium decreased in the head-up and head-down positions more than in the supine position (Fig. 3). This would indicate that cardiac filling pressure decreased in both the head-up and head-down position because of the hydrostatic column of blood. Pressures in the pleural and pericardial cavity, however, responded similarly, and transmural cardiac pressures did not change significantly.

Changes in body position would greatly affect capillary fluid filtration if changes of similar magnitude in the extravascular pressures did not counteract the changes in intravascular hydrostatic pressure. In addition regulatory mechanisms at the microvascular level control the tissue filtration rate. The important
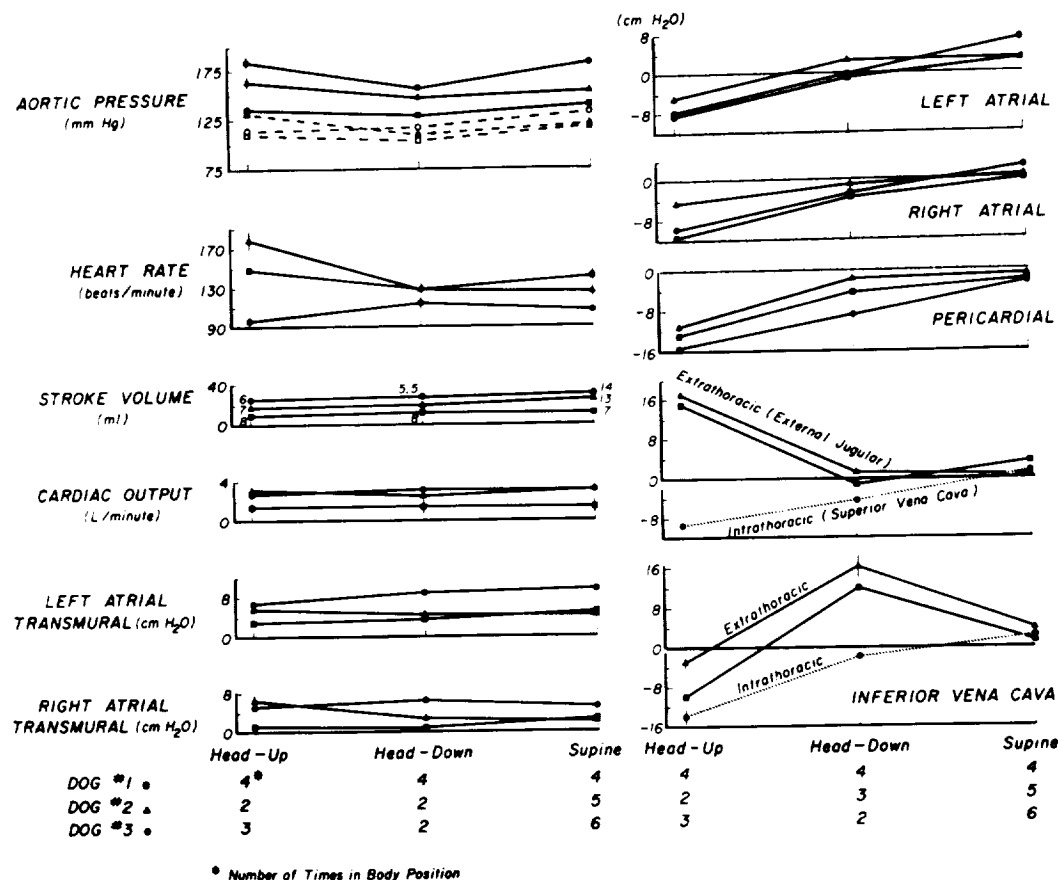
FIG. 3. Intrathoracic and venous pressure relationships and hemodynamic responses to changes in body position. Averages of right and left atrial transmural pressures, cardiac output, stroke volume, heart rate, and systemic pressures (*left*) and average abdominal vena cava, external jugular, pericardial, and right and left atrial pressures (*right*) in supine, head-down, and head-up position in 3 dogs. Adjacent to curves for stroke volume, number of cardiac-output measurements. [From Avasthey and Wood (11).]

role of venous pressure (P_v) in determining capillary pressure (P_c) can be stated as

$$P_c = P_v + R_v \cdot \frac{P_a - P_v}{R_a - R_v} \qquad (4)$$

where P_a is arterial pressure, R_a is arterial resistance, and R_v is venous resistance (136, 169). Maintenance of P_c determines the bulk movement of fluid in and out of the capillary network. Recent data (165, 235) suggest that local adjustments in the relationship of pre- to postcapillary resistance are important in the microvascular response to changes in hydrostatic loading. The local response of the pre- and postcapillary vessels may include a myogenic component of the smooth muscle cells of the vessel wall (168). The principal autoregulatory adjustments occur on the arteriolar rather than the venous side. The relative contribution of metabolic and myogenic mechanisms may be different in different vascular beds (168). A change from the supine to the upright position does not normally increase extracellular fluid in dependent regions enough to produce manifest edema. Transmural pressure tends to remain constant; any change is offset by an alteration in the pre- to postcapillary resistance to maintain P_c. In conditions such as heart failure, where dependent edema can occur, the underlying cause is the increase in the dynamic value of P_v.

Evidently several mechanisms modify the hydrostatic effects of posture changes in many regions of the cardiovascular system. The best example of a simple hydrostatic system in the human is the pulmonary circulation. Regional pulmonary blood flow in normal individuals at rest depends on the pressure in the pulmonary artery generated by the heart (dynamic pressure) and the hydrostatic pressure gradient in the column of blood in the lungs (static pressure). West (352) has convincingly shown that in the upright position the blood flow to the apex of the lung is less than the blood flow to the base of the lung. In the supine position the gradient in flow is from the superior (anterior) to the dependent (posterior) regions. Coulam and Wood (68) have found a simple hydrostatic fluid pressure gradient in the pleura as body position changes. These two findings imply that transmural pressure in the lungs varies with changes in the height of the hydrostatic fluid column relative to a reference point. Blood enters the system near the center of each lung, and this level may serve as a reference point. Increasing the gravitational field should accentuate the regional differences in pressure and flow in the direction of the gravitational force vector. Conversely, removing the gravitational force should shift pressure and flow toward superior regions, such as the apex in the upright position. This hypothesis has been tested by exposing humans to 0 *g* in a high-performance aircraft during parabolic flight (322). Pulmonary blood flow, measured with macroaggregated human serum albumin injected before and during the parabolic flight profile, was higher in the apical regions of the lungs (Fig. 4) during 0 *g* than during a seated 1-*g* control period.

## IMMEDIATE CARDIOVASCULAR RESPONSES TO POSTURE CHANGES AND BLOOD VOLUME REDISTRIBUTION

Experimental Conditions

The principal hemodynamic effect of posture change is redistribution of venous volume with marked secondary changes in ventricular filling and stroke volume. The magnitude of the volume shift is an important determinant of the physiological response. Experimental procedures that cause reproducible and quantifiable redistribution of volume are essential to the study of cardiovascular responses. Skeletal muscle activity in the legs markedly affects venous pressures and volumes (213, 214, 264). Muscle activity is difficult to control and monitor during standing. Studies of the mechanisms producing orthostatic cardiovascular changes in humans have therefore often been based on alternate methods that approximate the degree of venous pooling during standing but minimize muscle activity.

LOWER-BODY NEGATIVE PRESSURE. In aerospace medicine lower-body negative pressure (LBNP) has been used extensively as a research tool and clinical method (355). It has the inherent advantage of producing a gravity-independent redistribution of venous volume, and during space flight it can uncover changes in orthostatic tolerance (172). Furthermore during LBNP the subject remains at rest in the supine position, which facilitates physiological measurements and minimizes the likelihood of confounding activity in skeletal muscle. Measuring changes in leg volume is easy and can provide at least a semiquantitative measure of shifts in venous volume. Many different LBNP devices have been constructed, including metal cylinders and hemicylinders and wooden boxes. The bottom of the low-pressure chamber is usually fitted with a saddle to prevent movement into the device during suction. A rubber or plastic seal surrounds the subject and attaches to the opening of the LBNP chamber. The effective level of the seal is usually about the iliac crests. A commercial vacuum cleaner can produce the vacuum. A system including valves and a pressure gauge automatically or manually regulates the pressure. The degree of venous pooling is proportional to the negative pressure. In general LBNP at −50 mmHg, standing, and head-up tilt at + 70° similarly change heart rate and systolic pressure (355).

PASSIVE TILT. During passive tilt the subject rests on a table that can be rotated around an axis corresponding to a transverse body diameter, preferably at a level approximating the body's center of mass. A restraint system including a saddle prevents longitudinal changes in body position. The position of the table

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FIG. 4. Regional pulmonary blood flow at 1 *g* and 0 *g* at various lung levels. Measured in volunteer by injecting radioactive tracer during 0 *g* and in seated position at 1 *g*. Note flow shifts toward apex of lungs. Similar results in 6 subjects. Zero distance, apex of lung; opposite end of scale, toward base of lung. *Top*: control measurements; *Bottom*: 0-*g* measurements.
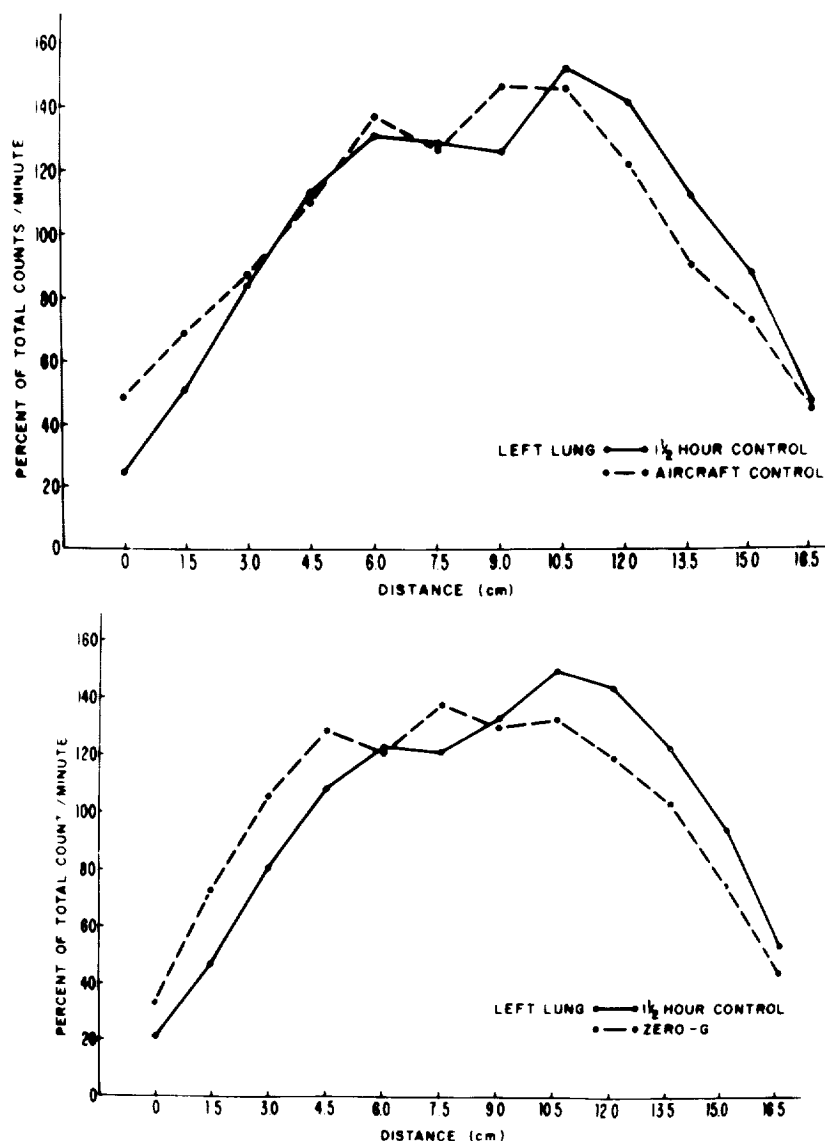
and the subject is usually specified in terms of angular deviation from the horizontal plane, positive for head-up and negative for head-down positions. The direct hydrostatic effects are proportional to the sine of the angle between the table and the horizontal plane, i.e., +30° produces 50% and +75° as much as 95% of the effects of a full 90° change from supine to upright.

IMMERSION. This intervention produces a marked central fluid shift. Water immersion has been used extensively as a therapeutic agent (hydrotherapy) since the beginning of history. More recently immersion has been applied to investigate the renal effects of a central redistribution of blood volume (16, 17, 87–90, 105, 108) and to simulate zero gravity (121, 122).

Epstein (87) has recently reviewed the technical and physiological aspects of immersion in detail, including conditions that may modify the cardiovascular response. The temperature of the bath is critical. Ther-

moregulatory mechanisms disturb the hydrostatic effects if the bath is not thermoneutral, i.e., kept at 33°C–35°C. Water is the common medium, but silicone fluid and saline minimize fluid exchange across the skin and prevent skin lesions due to maceration. The external application of hydrostatic pressure alters respiratory mechanics. Upright immersion is equivalent to negative-pressure breathing, which by itself has significant cardiovascular and renal effects that are directionally similar to the primary vascular hydrostatic effects.

G-SUIT DEVICES. Systems with inflatable rubber bladders compressing the legs and the abdomen, called G suits, have been widely used in aviation and recently also in emergency medicine to prevent venous pooling and produce a central blood volume shift in hypovolemic shock. Recent hemodynamic studies (103) have shown, however, that the primary effect is an increase

of systemic resistance rather than an increase in ventricular filling.

LOWER-BODY POSITIVE PRESSURE. Applied with a chamber analogous to an LBNP apparatus, lower-body positive pressure (LBPP) has been used to study the renal and hormonal responses to a central fluid shift in primates (239).

Blood Volume and Distribution

Total blood volume in mammals is an essentially linear function of total body weight, but there are fairly large species differences. Physically active animals generally have larger volumes than inactive animals. Mean values in normal adult humans cluster around 75 ml/kg body wt, or 5-5.5 liters for a 70-kg man. Sources of interindividual variations include body composition, age, climate, and physical activity (306).

Available estimates on the normal distribution of blood volume in the human are based on incomplete regional measurements and extrapolation from more precise measurements in experimental animals. Approximately 70% of the total blood volume is contained in the systemic veins; the heart and lungs account for about 15%, the systemic arteries for 10%, and the capillaries for 5% (107, 124, 298, 307). Hydrostatic pressure changes and regional variations in compliance are the primary determinants of the pattern of postural redistribution of intravascular volume. There are important modifiers, however, including the compliance of perivascular tissues, hydrostatic changes in tissue pressure, and myogenic and neurogenic effects on venous tone. Also vasomotor activity causes postural redistribution of venous volume (48, 53, 254, 277).

The term *compliance* is often applied without being rigorously defined. In common usage within this subject area, it is equivalent to the change in volume for a given pressure change (dV/dP) within the physiological pressure range. Nonlinearities in the pressure-volume relationship are often disregarded. The systemic veins supply most of the overall compliance of the cardiovascular system. Effective total vascular compliance, as derived from measurements of central venous pressure during acute changes in blood volume, is of the order 2-3 ml·mmHg^{-1}·kg^{-1} body wt in the human and dog (80, 108, 140, 189, 299). Measuring systemic vascular compliance in the intact subject is complicated by reflex-induced hemodynamic adjustments, delayed compliance (i.e., viscoelastic creep of vessel walls), and blood volume changes caused by tissue filtration (7, 358). Nevertheless the low-pressure compartment of the circulation, i.e., the systemic veins, the right heart, the pulmonary circulation, and the left atrium, which together contain 85% of the total blood volume, clearly contributes an even larger percent of total vascular compliance. The pulmonary veins account for most of the lung blood volume and the total compliance of the pulmonary circuit. The

pulmonary capillaries are relatively noncompliant (72, 86, 360). Total pulmonary vascular compliance in the rabbit is ~0.1 ml·mmHg^{-1}·kg^{-1} body wt (86). Compliance of the systemic arteries is lower by an order of magnitude, or ~0.01 ml·mmHg^{-1}·kg^{-1} body wt (80), which corresponds to less than 1% of the total vascular compliance.

Regional partition of the overall compliance is difficult because of nonlinearities of the basic vascular pressure-volume relationship, discontinuities in the distribution of venous pressures, and the inaccuracies inherent in in vivo measurements of regional blood volumes (138, 223, 277). The potential of volume measurements based on scintigraphic techniques is yet to be fully explored. Pressure measurements during pneumatic compression of the lower half of the body and during upright immersion (81, 189) suggest that the intrathoracic component of the low-pressure system contributes about 50% of total vascular compliance.

Changing from a supine to an upright position increases venous volume of the legs by about 500 ml (110). Most of the translocated volume is contained in the deep intra- and intermuscular leg veins (213, 214). Additional volume, probably 200-300 ml, is transferred to the veins in the buttocks and the pelvic area. It has been thought that the translocated volume is derived principally from the intrathoracic compartment of the low-pressure system (110, 305) because the hydrostatic counterpressure from the abdominal organs tends to minimize postural changes in transmural venous pressures and venous volume in the splanchnic area. Nevertheless reflex-induced splanchnic vasoconstriction (70, 354) probably produces a passive decrease in venous volume. Measurements based on radionuclear techniques suggest a large contribution also from the splanchnic region (220, 221).

Lower-body negative pressure at −40 to −50 mmHg and standing cause similar shifts in blood volume (355), but the distribution patterns within the lower half of the body are probably somewhat different. The primary pressure gradient along the longitudinal axis of the body (created by decrease in ambient pressure below seal) is stepwise rather than linear (as during standing) and is modified by the tissues surrounding the blood vessels. Wolthuis et al. (355) estimated changes in regional blood volumes and found no changes in plasma-bound isotope activity over the upper abdomen during LBNP at −40 mmHg, whereas the mean increase in activity over the foot, calf, thigh, buttock, and pelvis equaled 24%, 54%, 49%, 39%, and 20%. This heterogeneity can be at least partially attributed to regional differences in the ratio between soft and bony tissues.

There is little quantitative information on the acute intravascular volume shifts during head-down tilt. Significant leg volume changes—as large as during orthostasis—occur during the initial hours after a change from supine to 5° head-down tilt (37). The magnitude
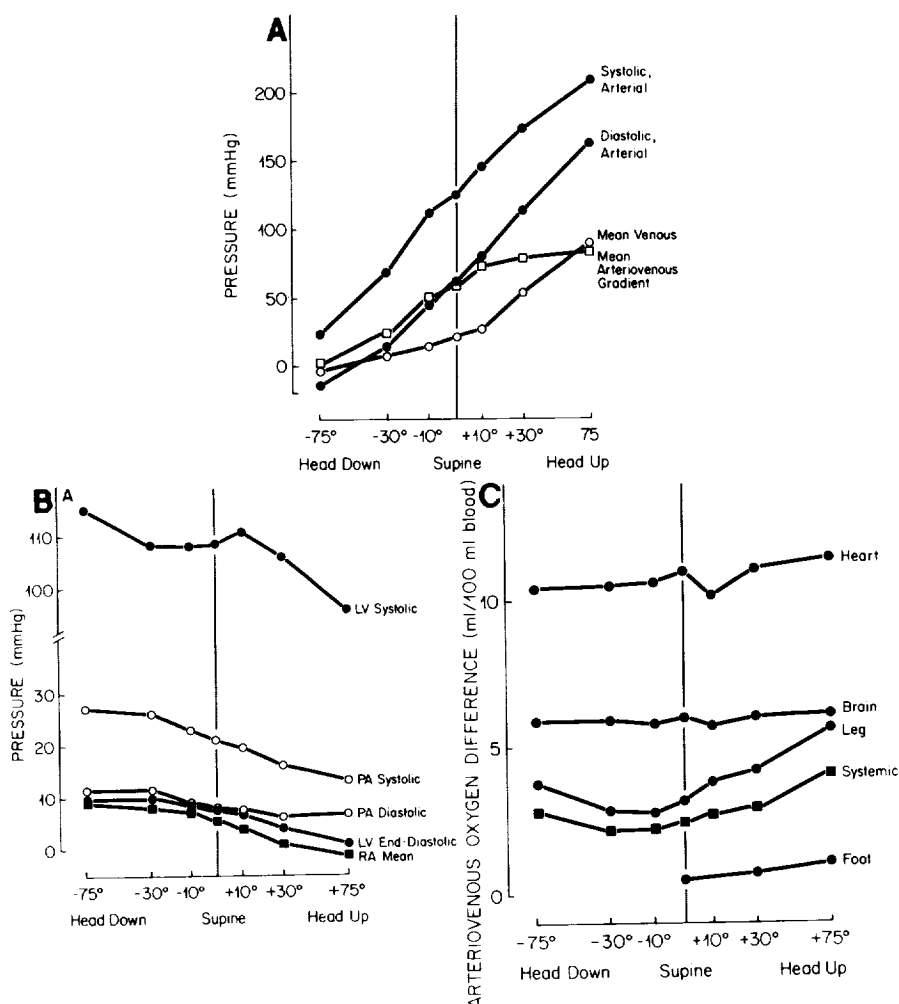
FIG. 5. Responses to graded head-up and head-down tilt in 10 humans. LV, left ventricle; PA, pulmonary artery; RA, right atrium. Intravascular pressures in foot (A) and in central circulation (B), and regional and systemic arteriovenous O_2 differences (C). Angle of tilt (horizontal axis) plotted as sine function to provide linear scale for primary hydrostatic effects of body-position changes. [Based on data from Katkov and Chestukhin (178).]

of the fluid shift during immersion depends on depth and body position. Supine head-out immersion produces no significant acute hemodynamic effects (18) and presumably only insignificant volume shifts. Upright immersion to the level of the diaphragm abolishes the hemodynamic changes that are normally associated with standing. The hemodynamic state is similar to that at rest supine (269). Upright immersion to the level of the neck reverses the normal peripheral orthostatic redistribution of blood volume and increases central blood volume (as determined by indicator-dilution technique) by some 700 ml (4). Farhi and Linnarsson (95) have also demonstrated progressive but nonlinear hemodynamic changes as immersion depth increased.

Intravascular and Intracardiac Pressures

Actual postural pressure changes within the arterial system closely conform to alterations in the hydro-

static pressure component as predicted from the change in vertical distance between the point of pressure measurement and the reference point. Katkov and Chestukhin (178) directly measured pressure at tilt-table positions ranging from +75° head up to −75° head down (see mean data in Fig. 5). In the foot, systolic arterial pressures in these two positional extremes differed by 188 mmHg, which is remarkably close to the expected hydrostatic gradient of 195 mmHg (as calculated from data on distance between right atrium and foot, angle of tilt, and sp gr of blood).

Thin walls and valves make the systemic veins much more complicated than the arteries. Venous pressures in the foot of supine humans are 10-15 mmHg (110, 178). There is a decrease of 2-3 mmHg from the foot to the inferior vena cava at the level immediately below the diaphragm. An additional sharp pressure drop of 2-3 mmHg accompanies entry into the thoracic cavity. A similar gradient is recorded at the thoracic inlet when a catheter is passed from the internal

jugular vein into the superior vena cava (9, 110). The stepwise change in intravascular pressure has the same order of magnitude as the average negative pleural pressure during quiet respiration at rest (232), suggesting that there is little change in transmural venous pressure.

A transition from a supine to an upright position introduces significant nonlinearities. The intravenous pressure distribution (as referred to the level of the right atrium) deviates markedly from the predicted distribution in a simple and uniform closed hydrostatic system, particularly in the regions cephalad to the heart. Even at negative intravascular pressure the intracranial veins are kept open by periosteal adhesions and by parallel hydrostatic pressure changes in the cerebrospinal fluid. Pressures at the level of the thoracic inlet change from a few mmHg positive pressure in the supine position to about 8–10 mmHg negative pressure in the standing position. The neck veins and even the upper part of the superior vena cava collapse in erect normal human subjects, causing a discontinuity in the pressure distribution. The jugular veins form a separate hydrostatic column within which pressures during orthostasis are independent of the right atrial pressure (9, 178).

Deviations from a simple hydrostatic pattern are evident also in the leg veins (Fig. 5). Early postural venous changes in the foot are significantly smaller than the corresponding arterial changes during head-up and head-down tilt. The relationship of the intravenous pressure to the height of the hydrostatic column is curvilinear (178). The data suggest a partial collapse of the leg veins in the head-down position and a significant effect of the venous valves during head-up tilt. However, the valves cannot support the full hydrostatic pressure in the upright position and eventually become incompetent as the veins are distended (151, 182). The collapse of the veins above the level of the heart is also likely to modify lower-body intravenous pressures in the upright position. Part of the venous hydrostatic column is supported by the elastic forces of the intrathoracic tissues as diagrammed in Figure 1C. There is no convincing evidence for venous collapse at the level of the diaphragm (110).

Immediate postural changes in mean atrial and end-diastolic ventricular pressures are essentially linearly related to the hydrostatic component over the entire range from full head-up to head-down tilt with the exception of little or no increase at an angle steeper than −30° head down (see Fig. 5). The difference between the extreme positions is about 10 mmHg. Right and left ventricular filling pressures change in parallel (178). Several investigators (21–24, 119, 120, 328, 329) have reported similar or slightly smaller changes in filling pressures after a transition from supine to sitting or standing (Table 1) and from supine to moderate degrees of head-down tilt (37, 250).

These measurements of intracardiac and central venous pressures may not accurately reflect the postural changes in effective or transmural filling pres-

TABLE 1. *Direct Hemodynamic Measurements in Normal Subjects at Rest*

Parameter	Supine	Sitting	P
Heart rate, beats/min	73 ± 4	84 ± 4	<0.001
Pressure, mmHg			
Brachial artery	96 ± 3	99 ± 4	
Systolic	130 ± 5	132 ± 5	
Diastolic	76 ± 3	82 ± 3	<0.05
Pulmonary artery	13 ± 1	13 ± 1	
Pulmonary capillary wedge	6 ± 1	4 ± 1	<0.001
Left ventricular end diastolic	8 ± 1	4 ± 1	<0.001
Stroke index, ml/m^2	50 ± 5	35 ± 3	<0.001
Cardiac index, liters·min^{-1}·m^{-2}	3.5 ± 0.3	2.8 ± 0.2	<0.001

Means ± SE for 10 sedentary men, age 32–58.   [From Thadani and Parker (328).]

sures; the effect of posture on pleural and pericardial pressures should also be considered. Such pressure changes—as discussed in HYDROSTATIC PRESSURE, p. 1025—have been studied in the anesthetized dog (10, 68). The pleura and pericardium behaved much like a simple hydrostatic system. The transmural atrial pressures recorded in the head-up and head-down position did not differ significantly, and cardiac output did not change. The extent to which these findings apply to humans is unknown. Measurements of cardiac dimensions and performance provide overwhelming, if indirect, evidence for significant postural changes in the effective filling pressures in the human. Significant concurrent changes in intrinsic or effective transmural ventricular compliance are unlikely. The different responses in intact humans and anesthetized animals may be due to different locations of the HIP, different extracardiac hydrostatic conditions, reflex activity, or a combination of these factors.

Head-out upright immersion produces an increase in central venous pressure that is proportional to the depth and that averages 10–13 mmHg above the normal standing level (4, 81, 269). Applying LBNP at −40 to −50 mmHg causes a decrease in central venous pressure similar to that during a change from the supine to upright position (37, 167, 244, 250, 355).

Cardiac Dimensions and Pump Performance

The principles governing cardiac pump performance to a large extent determine the cardiovascular responses to changes in posture. Comprehensive analysis of ventricular function includes simultaneous consideration of force, velocity, and fiber length (238). The velocity axis can often be disregarded without serious loss of information in the analysis of the performance of the intact heart. The ventricular pressure-volume relationship (133, 286, 324, 347) is useful for analysis and links muscle mechanics and ventricular function. Contractile state is defined as the maximal tension or pressure that can be developed at any given fiber length or volume. Maximal ventricular pressure is normally a linear function of volume. The amount of shortening or stroke volume that can be achieved from

any given fiber length or volume can be increased only by reducing afterload or enhancing the contractile state. Similarly an increase in the amount of shortening at a given afterload requires either an increased end-diastolic volume or an increased contractile state. Decreased filling pressure, e.g., caused by venous pooling during the transition from the supine to standing position, therefore causes stroke volume to decrease unless compensated for by an increased contractile state or decreased afterload. However, the systolic reserve capacity of the normal human heart is limited. The left ventricular ejection fraction at rest is about 70%. Powerful reflex mechanisms maintain arterial pressure and afterload. A large decrease in preload therefore inevitably decreases stroke volume. Cardiac output can only be maintained by increasing heart rate.

There is ample evidence that postural changes produce significant changes in the dimensions of the heart. Studies based on single or biplane X-rays have demonstrated a decrease in total heart size after a change from the supine to standing position. Although there are fairly large interindividual variations, the average decrease in an adult normal man is 100–200 ml, or 10%–20% of normal total heart volume of up to 500 ml/m² body surface area (152, 176, 245).

More recently, noninvasive imaging methods have provided detailed data on cardiac dimensions and performance in humans. A calibrated nongeometric scintigraphic technique measured left ventricular volumes supine and sitting (Table 2). The relative change in left ventricular end-diastolic volume was of similar magnitude to that in total heart volume. Ejection fraction and end-systolic volume did not change significantly. Thus the postural decrease in stroke volume was primarily caused by a reduced preload. Nixon, Blomqvist, et al. (251) used M-mode echocardiography to study the left ventricle at supine rest, during LBNP at −40 mmHg and head-down tilt at −5°. These interventions significantly decreased the estimated end-diastolic volume 28% during LBNP and increased it 23% during head-down tilt. There were only small changes in ejection fraction with an increase during head-down tilt and a decrease during LBNP but large

TABLE 2. *Left Ventricular Dimensions and Performance at Rest*

Parameter	Supine	Sitting	P
Volume, ml			
End diastolic	107 ± 10	85 ± 6	<0.02
End systolic	34 ± 4	32 ± 5	
Stroke	76 ± 8	55 ± 5	<0.05
Ejection fraction, %	76 ± 2	72 ± 4	
Heart rate, beats/min	71 ± 6	89 ± 5	<0.05
Arterial pressure, mmHg			
Systolic	125 ± 8	125 ± 5	
Diastolic	76 ± 4	84 ± 4	

Means ± SE for 7 normal subjects.   [Scintigraphic data from Poliner, Blomqvist, et al. (262), by permission of the American Heart Association, Inc.]

effects on stroke volume (+35% and −33%). The heart rate and arterial pressures remained stable, and the velocity of circumferential fiber shortening did not change. These data are also consistent with a marked preload effect on ventricular performance with little change in contractile state. Sandler et al. (292) and Ahmad, Blomqvist, et al. (5) have reported similar results during LBNP.

Parker and Case (259) recently suggested that the normal human left ventricle operates at or near its maximal functional size at rest in the supine position, but data obtained during head-down tilt (250, 251), supine exercise (262), and immersion clearly indicate a diastolic reserve capacity. The increased central venous pressure during upright immersion is associated with a large increase in heart size and stroke volume (4, 18, 40, 81, 95, 195, 269).

Cardiac Output

Thadani and Parker (328) studied hemodynamics in normal sedentary sitting and supine men (see Table 1). Many other investigators (21, 24, 119, 120, 287, 309, 345) have reported similar results. Stroke volume decreases in the upright position by about 33%. The modest increase in heart rate does not fully compensate for the decrease in stroke volume. Therefore cardiac output decreases by about 20%. Mean arterial pressure is maintained and systemic resistance increases in direct proportion to the fall in cardiac output. The systemic arteriovenous oxygen difference also increases. A change from the supine to standing position causes qualitatively similar but slightly larger hemodynamic adjustments than a change from the supine to sitting position (23, 24). Matalon and Farhi (224) demonstrated an inverse linear relationship between cardiac output and the sine of the tilting angle during passive head-up tilt.

Blomqvist et al. (37) found that head-down tilt at −5° does not change arterial pressure or cardiac output but produces an early and transient increase in stroke volume, which causes compensatory bradycardia. Katkov et al. (179) recorded no significant change in right ventricular end-diastolic pressure but a 15% increase in stroke volume after 15 min at −20° head-down tilt. There was a small increase in heart rate, and cardiac output increased by 27%. The lack of change in right ventricular pressure at −20° may seem paradoxical, but experimental data indicate that a steep head-down tilt may decrease filling pressures (110). Upright immersion increases cardiac output by 30% or more, mainly because of an increase in stroke volume without any compensatory bradycardia (4, 18).

Regional Flow

The data on arteriovenous oxygen differences presented in Figure 1 indicate that flow to vital organs, i.e., the brain and the myocardium, remains adequate over the entire range of short-term postural chal-

lenges. Changes in posture, however, produce a complex set of regional adjustments.

BRAIN. The oxygen uptake of the brain changes little unless there are functional disturbances of clinical significance (197). Oxygen delivery to the brain is generally well protected during gravitational stresses, perhaps better in humans than in other species (240). Several factors combine to minimize the effects of gravity during postural changes and during acceleration (146), including an efficient autoregulation of blood flow, hydrostatic pressure changes in the cerebrospinal fluid (which are likely to parallel intravascular changes, particularly in arterial pressure), and the architectural and functional characteristics of the intracranial veins. Mean arterial pressure at eye level during tilting or hemorrhage can fall below 30 mmHg before consciousness is seriously impaired and below 25 mmHg before syncope develops (146, 193). The basic efficiency of this system does not necessarily preclude significant postural changes in total cerebral flow (197), but Katkov, Chestukhin, et al. (178, 179) found an essentially stable arteriovenous oxygen difference over the entire range of body positions from −75° to +75° (Fig. 2).

MYOCARDIUM. Changes in arterial pressures, heart rate, contractile state, and ventricular dimensions during posture changes are likely to change myocardial oxygen demand and perfusion. Langou et al. (196) found that head-up tilt at +30° decreased left ventricular end-diastolic diameter, myocardial oxygen uptake, and coronary flow in dogs. The arteriovenous oxygen difference across the myocardium also decreased. Neither the heart rate nor the contractile state changed. Similar detailed data on flow and oxygen demand in the human are unavailable. Katkov and Chestukhin (178) recorded no changes in myocardial oxygen extraction in their human subjects during head-up and head-down tilt.

SKIN AND MUSCLE. The effects of postural changes on blood flow to the resting arm and leg are directionally similar to the changes in overall systemic flow. Increasing degrees of venous pooling during LBNP cause a gradual and sustained reduction of forearm flow (167, 231, 271, 362). The relative importance of muscular and cutaneous vasoconstriction is controversial. Several investigators have concluded that the orthostatic vasoconstrictor response in resting skeletal muscle probably accounts for a major portion of limb flow reduction (8, 12, 128). McNamara (231) found only transient decreases in hand blood flow (primarily cutaneous) during mild degrees of LBNP. More severe LBNP stress caused a sustained flow reduction with no quantitative relation to the degree of venous pooling. Gauer and Thron (110) reviewed several series of experiments and also concluded that the orthostatic vasoconstrictor response in the leg primarily involved skeletal muscle with little or no contribution from the cutaneous circulation. On the other hand Rowell et al.

(282) attributed the decrease in forearm flow during LBNP equally to vasoconstriction in skin and muscle, consistent with significant baroceptor-mediated effects also on the cutaneous circulation (279).

McNamara et al. (231) noted the similarity between the peripheral responses to head-up tilt and LBNP, which imply that changes in systemic flow and reflex adjustments are more important determinants of limb blood flow than the direct hydrostatic effects. However, hydrostatic effects are evident during extreme degrees of head-down tilt. Katkov and Chestukhin (178) found that blood flow to the foot approached zero in the −75° head-down position.

SPLANCHNIC REGION. The splanchnic bed is a major source from which blood flow and venous volume can be redistributed to other areas during stress. The liver and the splanchnic area contain about 25% of the total blood volume and receive an equally large portion of cardiac output at rest, but they extract less than 20% of the available oxygen (278). Progressive peripheral pooling during LBNP gradually reduces splanchnic flow. Flow rates at −40 mmHg are less than 70% of control (1, 167).

KIDNEYS. The kidneys receive about 20% of the total systemic flow at rest. Orthostatic stress significantly reduces renal plasma flow, as judged from changes in p-aminohippuric acid clearance. Head-up tilt at 45° reduces renal flow to about 50% of the supine rate (295, 351). Gilbert et al. (113) reported a 27% reduction in effective renal plasma flow during LBNP at −60 mmHg. In contrast the increased cardiac output during upright immersion does not consistently change renal hemodynamics (87, 88).

Postural Effects on Hemodynamic Responses to Exercise

Many of the postural hemodynamic effects that are evident at rest persist during exercise. Cardiac output is 1-2 liters/min higher in the supine than in the sitting position at rest and during dynamic exercise involving large muscle groups, e.g., bicycle exercise (21-24, 85, 328, 329). Body position does not affect the slope of the normal linear relationship between oxygen uptake and cardiac output. An increase in oxygen uptake of 1 liter/min is associated with an increase in cardiac output of about 6 liters/min in both positions. Thus the systemic arteriovenous oxygen difference is wider in the upright than in the supine position. Total systemic resistance is higher in the upright position at rest and during low-level submaximal exercise, but the differences are abolished during heavy submaximal work (22).

Stroke volume at rest is significantly larger and heart rate is lower in the supine position, but transition from rest to exercise causes a larger stroke volume increase in the upright position (21-24, 328, 345). Heavy leg exercise tends to abolish the positional stroke volume differences. The postural effects tend to

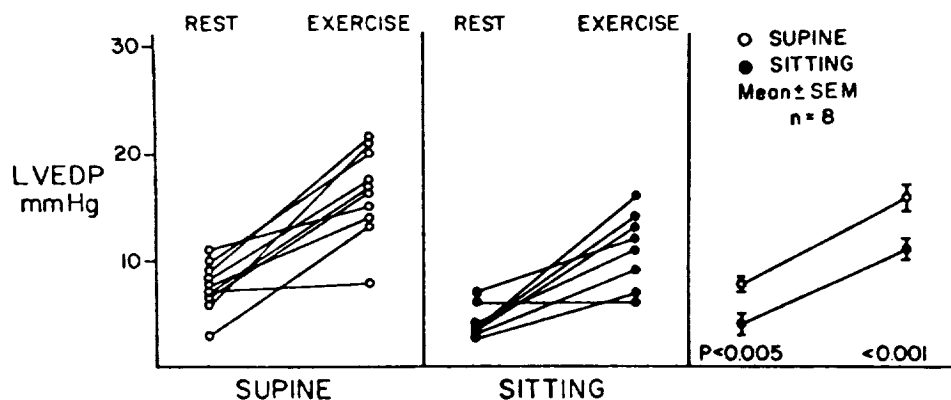1036 HANDBOOK OF PHYSIOLOGY ~ THE CARDIOVASCULAR SYSTEM III

FIG. 6. Normal individual and group mean values of left ventricular end-diastolic pressure (LVEDP) in supine and sitting positions at rest and during exercise. [From Thadani and Parker (328).]

be larger during dynamic exercise with small muscle groups; e.g., arm exercise and stroke volumes are different also at maximal work levels. Relative tachycardia maintains a normal slope of the relationship between oxygen uptake and cardiac output, but absolute flows are 1-2 liters/min below supine levels also during arm exercise (22).

Right and left ventricular filling pressures are higher at rest in the supine position. According to most (85, 119, 120, 328) but not all (117, 276) investigators, exercise in either position progressively increases left ventricular filling pressures, but pressures remain higher in the supine position (Fig. 6). Mean right atrial and right ventricular end-diastolic pressures as referred to the atmosphere tend to remain unchanged or actually decline during exercise (22, 85). Mean pleural pressures, however, become increasingly negative with increasing ventilation and may average −10 mmHg during heavy exercise (232). This means that both right- and left-sided effective filling pressures probably increase during exercise but that the changes are larger in the left ventricle.

As discussed earlier in this section there is ample evidence that at rest left ventricular diastolic volume is larger in the supine than in the upright position. The increase in stroke volume that occurs between rest and exercise in the upright position is associated with an increase in total heart size and left ventricular end-diastolic volume (69, 152, 285). There is general agreement that end-systolic volume decreases during exercise in both body positions (46, 69, 117). The role of the Starling mechanism during exercise in the supine position is controversial (46, 69, 117, 296, 311, 348), however, perhaps because of methodological limitations. Poliner, Blomqvist, et al. (262), who used a quantitative nongeometric scintigraphic method to circumvent many of the problems inherent in echocardiography, contrast ventriculography, and the use of epicardial markers, found a significant increase in end-diastolic volume during supine exercise. Left ventricular end-diastolic volumes were higher in the supine position at rest as well as during submaximal and

TABLE 3. *Hemodynamic Effects of Acceleration*

Acceleration	Cardiac Output	Heart Rate	Stroke Volume	Mean Arterial Pressure
G_z				
+2	+7	+14	−24	+9
+3	−18	+35	−37	+21
+4	−22	+56	−49	+27
G_x				
+2	−12	−2	−10	+11
+3.5	+9	+17	−7	+18
+5	+27	+40	−8	+25

Effects of head-to-foot (+G_z) and transverse gravitational force (+G_x) acceleration in 6 relaxed human volunteers. Values are % change from control. [Data from Lindberg et al. (207, 208).]

maximal exercise. End-systolic volume was slightly smaller in the upright position, and maximal stroke volumes were similar (Table 3; Fig. 7). These data are consistent with a combined Starling effect and increased contractile state during exercise, both supine and upright.

The lower systemic arteriovenous oxygen difference during exercise in the supine position indicates a higher perfusion rate of inactive tissue. Blood flow in working limbs is more complex. During leg exercise limb flows are higher, and after exercise they are lower in the upright than in the supine position (98, 99, 206). Greenleaf et al. (128) published exercise data that partially disagree, but their flow data were obtained immediately after exercise. Folkow et al. (98, 99) attributed the higher flow to a higher driving pressure in the upright position. A large hydrostatic component affects intravascular pressures in a dependent limb, but the reduction in venous pressure due to skeletal muscle activity is probably particularly prominent there. The arteriovenous pressure gradient and the perfusion pressure therefore tend to be greater when the working limb is dependent rather than at the level of the heart. Lind et al. (206) studied isometric exercise and found no postural effects on strength, arterial and right atrial pressures, or heart rate, but forearm flow increased and endurance improved in the upright po-
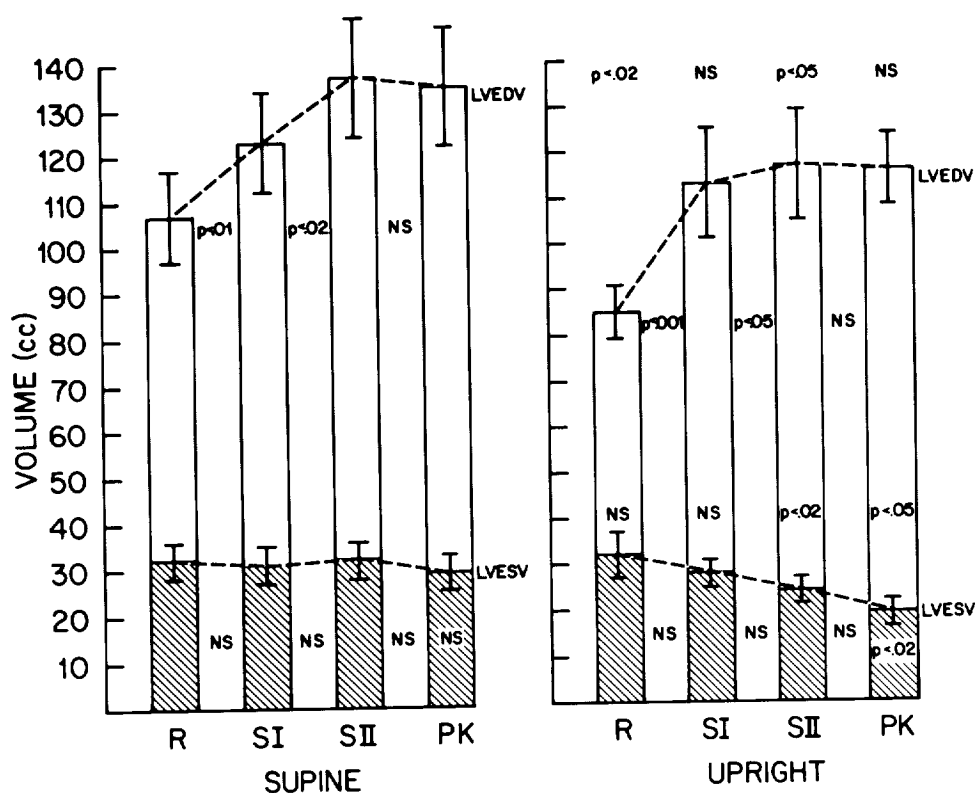
FIG. 7. Left ventricular end-systolic volume (LVESV; shaded portion), LVEDV (means ± SE; tops of *bars*), and LV stroke volume (clear portion) at rest (R) and during 3 levels of exercise (SI, SII, PK). Above *bars* of *right panel*, P values for corresponding upright and supine measurements of LVEDV at each work load; P values above LVESV data for corresponding supine measurements of LVESV; P values between adjacent *bars* for change between progressive work loads; P values in small boxes of peak exercise (PK) *bars* for change from R to PK for LVESV in each position. Between R and PK, LVEDV also increased significantly in both positions ($P < 0.001$ supine, $P < 0.02$ upright). SI, low-level work (300 kpm/min); SII, intermediate-level work (600–750 kpm/min). [From Poliner, Blomqvist, et al. (262), by permission of the American Heart Association, Inc.]

sition. No muscle pump is active during isometric exercise, and the position of the arm relative to the heart was similar in both body positions. These results are consistent with important neural rather than hydrostatic mechanisms. Lind et al. (206) discounted activation of the low-pressure baroceptor as a possible factor affecting peripheral flow. However, other investigators (2, 281) have found evidence for interaction during exercise between impulses originating in muscle receptors and in cardiopulmonary and carotid baroceptors. The upright position apparently modifies the inhibitory drive generated by the baroceptors (2). Bonde-Petersen et al. (41) showed larger systemic pressor responses to isometric knee extension and handgrip in the upright than in the supine position. The apparent disagreement between the absence of right atrial pressure changes reported by Lind et al. (206) and the conclusions of Abboud et al. (2) may be resolved by postulating significant changes in left-sided atrial and ventricular pressures during exercise.

There are no direct data on postural effects of myocardial blood flow during exercise in humans. However, patients with limited flow caused by coro-

nary disease provide evidence for a more favorable relationship between total body and myocardial work in the upright than in the supine position (196, 201, 329). Patients with effort-induced angina pectoris have a highly reproducible threshold of myocardial ischemia, i.e., the point at which myocardial oxygen demand exceeds the supply. The product of heart rate and systolic blood pressure reliably estimates myocardial oxygen demand if there are no major variations in left ventricular volume. The rate-pressure product at the onset of the angina pectoris is higher in the upright than in the supine position, probably because left ventricular filling pressures and volumes are lower (329). Wall tension and myocardial oxygen demand at any given left ventricular pressure are therefore higher during supine exercise.

Dynamic Responses to Posture Changes

REGULATORY MECHANISMS. Gauer argued forcefully that in humans the upright position is the normal reference and that basic vascular pressure-volume characteristics are regulated to provide optimal tissue

perfusion in the upright position (110). Nevertheless the supine position continues to serve as the basal or control state in most human hemodynamic studies. Few investigators have concerned themselves with the immediate circulatory adjustments to a change from a standing or sitting to a lying position. Careful study would probably reveal hysteresis; however, for the purposes of this discussion it is assumed that the hemodynamic responses to the supine-standing and standing-supine transitions are mirror images.

Multiple mechanisms determine the dynamic responses to changes in posture, including neurogenic control mechanisms and the functional characteristics of the veins. The redistribution of intravascular fluid produces reflex responses that primarily involve three different sets of receptors (49, 79, 188, 219, 257, 298, 333, 334): *1*) carotid and aortic mechanoreceptors, *2*) cardiopulmonary mechanoreceptors, and *3*) hypothalamic osmoreceptors and angiotensin II receptors. The third group of receptors interacts with the first two in the control of blood volume and is a less important determinant of the acute responses. Angiotensin II release can stimulate the central nervous system and augment sympathetic vaso- and venoconstriction, but the direct and indirect hemodynamic effects are physiologically important only in the sodium-depleted state (97, 298). Activating the cardiopulmonary mechanoreceptors by distension inhibits both antidiuretic hormone (ADH) and renin-aldosterone and produces a diuresis (87, 89, 90, 107).

Carotid and aortic mechanoreceptors. The mechanoreceptors in the walls of the carotid sinus and the aortic arch are stretch receptors. The degree of deformation and the rate of impulse flow are functions of transmural pressure. Afferent impulses travel in rapidly conducting myelinated and slowly conducting unmyelinated nerves with the glossopharyngeal nerve and the vagus to the cardiovascular centers. Efferent fibers reach the sinus and atrioventricular nodes, the ventricles, veins, and arterioles by vagal and spinal cord pathways. A fall in arterial pressure decreases afferent nerve activity and releases inhibitory activity in the cardiovascular centers. This results in increased heart rate and contractility, vaso- and venoconstriction, and reduced blood flow to the skin and skeletal muscle, the kidney, and the splanchnic region. Increased metabolic demands increase myocardial flow.

Cardiopulmonary mechanoreceptors. At least two sets of mechanoreceptors respond to changes in the intracardiac pressures (see chapter by Bishop et al. in this *Handbook* and refs. 49, 76, 79, 209, 218, 257, 333, 334): *1*) discrete endocardial receptors at the junctions of the superior and inferior vena cava with the right atrium and the pulmonary veins with the left atrium, which are connected to the cardiovascular center by myelinated vagal fibers and *2*) a diffuse receptor network of unmyelinated vagal fibers (C fibers) connecting all chambers of the heart with the cardiovascular centers. A similarly diffuse network of receptors with

afferent sympathetic spinal cord fibers form a third set. The functions of the members of this group are largely unknown although some are probably pain receptors.

Activation by deformation of both discrete and diffuse receptors affects renal sympathetic drive (decrease) and renal blood flow (increase) identically, but the heart-rate effects are opposite. Increased stretch of the discrete venoatrial receptors causes tachycardia; increased stretch of the diffuse receptors (and of the carotid sinus/aortic arch receptors) causes bradycardia. The left ventricular receptors increase their inhibitory activity whenever cardiac diastolic filling is augmented, whereas dilating the right ventricle has little effect (255, 334). Reciprocal variations in atrial and ventricular/arterial pressures, e.g., high mean atrial and diastolic ventricular pressures and low arterial pressures, as in severe congestive heart failure, tend to minimize the systemic impact of impulses from the combined receptor system (76).

Local reflexes. Local reflex mechanisms may also contribute to the response to orthostatic stress. Henriksen (143, 144) has demonstrated vasoconstriction with decreased limb blood flow in response to local venous distension. Blocking studies indicated that the vasoconstriction was mediated by a local (axonal) sympathetic reflex mechanism. Activation of venous afferent fibers producing reflex-induced leg muscle activity may also counteract postural pooling (330, 331).

Regulation of venous system. Passive and active control mechanisms combine to regulate central venous pressure and the regional distribution of venous volume. Passive volume changes, which dominate in the pulmonary vasculature, are a function of changes in the effective transmural distending pressure, i.e., the difference between intravenous pressure and tissue pressure. Arterial pressure and arteriolar resistance, the pressure in the right atrium and central veins, and the hydrostatic load in turn determine venous pressure. The downstream pressure gradients within the venous system (disregarding hydrostatic pressures) are small, 10 mmHg or less. Therefore the venous component of total peripheral resistance is small and arteriolar pressure is the major determinant of distending pressure and, indirectly, of venous volume. Arteriolar dilatation increases venous pressure and volume. Vasoconstriction has the opposite effect and displaces venous volume centrally (277).

Cardiovascular reflexes and circulating catecholamines mediate active changes in venous capacity. The level of α-adrenergic stimulation is the primary control mechanism. The basic muscle length-tension relationship, which applies also to the venous wall, makes active regulation more effective. A distended vein contracts more effectively when stimulated than a nearly empty vessel (7, 254, 297, 298). Volume changes at low venous pressures are primarily passive, whereas active venomotor mechanisms dominate at
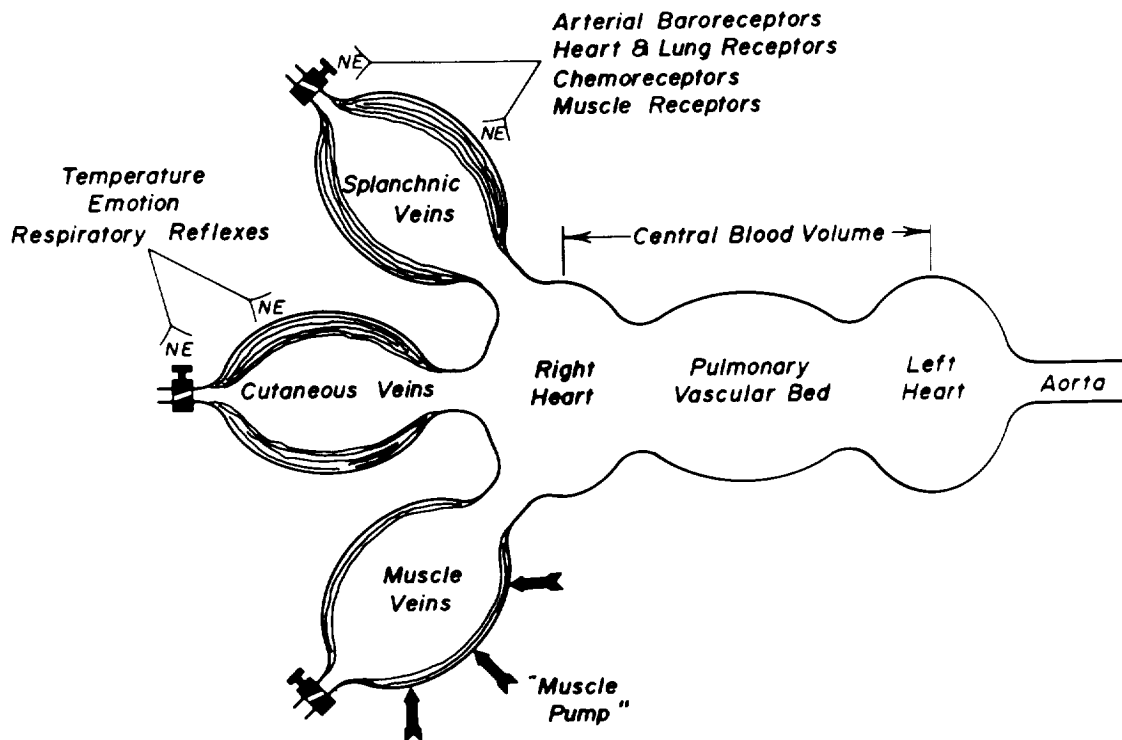
FIG. 8. Control of central blood volume and cardiac filling pressure by systemic veins. Contracting smooth muscle cells of venous wall, splanchnic veins in particular, actively changes filling of heart. Cutaneous veins mainly react to changes in temperature. Any change in distending pressure, whether due to gravity or changes in arteriolar resistance, passively changes capacity. NE, norepinephrine. [From *The Human Cardiovascular System*, 1979, by Shepherd and Vanhoutte (298), by permission of Raven Press, NY.]

high distending pressures (254). The importance of true autoregulatory changes (Bayliss effect) with increased myogenic activity in response to increased intravascular pressure is controversial (234). The opposite effect, i.e., relaxation after a prolonged increase in distending pressure (delayed compliance or viscoelastic creep), may be significant (358). By decreasing venous resistance due to relaxation of sphincters, e.g., in the hepatic vein, β-adrenergic stimulation may centrally displace venous volume (163).

Veins react differently to active stimulation (Fig. 8). Muscle veins respond weakly, if at all, to neural stimulation, including baroceptor-mediated reflexes. The capacitance of the cutaneous veins is primarily determined by the thermoregulatory stimuli. They dilate when temperature is increased, whereas deep limb veins dilate when perfused with cold blood (297). The splanchnic veins dilate when carotid and cardiopulmonary receptors are stimulated and contract when the muscle receptors (e.g., during exercise) and the chemoreceptors of the carotid body are activated (138, 297). Whether active venoconstriction is a determinant of acute postural hemodynamic responses is questionable. Gauer and Thron (110) thought that venoconstriction was not significant during orthostasis. Samueloff et al. (289) have shown only a weak and transient constriction of cutaneous veins at the onset

of LBNP at −60 mmHg. However, passive changes in venous volume caused by the splanchnic and peripheral vasoconstriction are probably significant (48, 70, 354).

SYSTEMIC RESPONSES. Figure 9 shows the principal cardiovascular responses to LBNP. As discussed in LOWER-BODY NEGATIVE PRESSURE, p. 1029, and SKIN AND MUSCLE, p. 1035, there is evidence that the responses to LBNP, standing, and head-up tilt $\geq 70°$ are qualitatively and quantitatively similar. The diagram comprises data from several series (5, 96, 100–102, 166, 167, 241–244, 250, 251, 266, 267, 280, 362). Linear interpolation compensated for differences between protocols for stepwise application of LBNP and gave uniform intermediate data points.

The degree of venous pooling is linearly related to the negative pressure. Left ventricular end-diastolic volume and stroke volume also decrease in a linear fashion to a level 25%–50% below that at rest. Cardiac output decreases 20%–40% (5, 100–102, 250, 266, 267). Initially heart rate and arterial pressure do not change. Peripheral and splanchnic arteriolar constriction compensate for the decrease in systemic flow. Progressive peripheral venous pooling eventually causes tachycardia, and the heart rate changes are closely linked to changes in arterial pulse pressure (167). The myocar-

FIG. 9. Principal features of human response to progressive lower-body negative pressure.
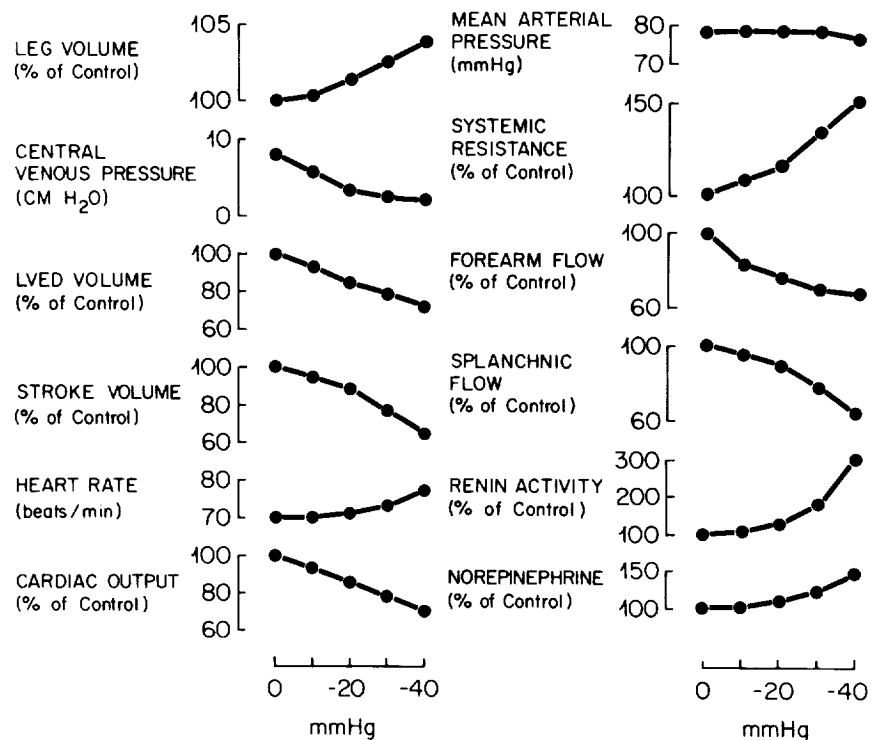
dial contractile state does not change until tachycardia develops. Thus the primary cardiac response is a negative Starling effect. An increase in plasma renin is apparent after about 2 min, and there are parallel changes in plasma norepinephrine (F. A. Gaffney, unpublished observations).

The combined data are consistent with a generalized vasoconstriction in response to decreased intracardiac pressures and volumes mediated by a decreased level of stimulation of cardiopulmonary receptors and reflex α-adrenergic stimulation. Increased sympathetic drive produces decreased renal blood flow and a release of renin. Progressive pooling with decreasing stroke volume and cardiac output eventually causes a fall in arterial pressure with compensatory tachycardia, increased contractility, and further vasoconstriction mediated by the arterial baroceptors. An increase in plasma catecholamines reflects sympathetic activation. Ewing et al. (94) thought that primarily vagal withdrawal mediated the early orthostatic heart-rate response, but data on autonomic blockade during head-up tilt or LBNP indicate that the true reflex response consists of a combined α- and β-adrenergic activation and vagal withdrawal (34-36, 211, 242, 293, 349). β-Adrenergic blockade attenuates the heart-rate response, and vagal withdrawal only partially compensates. The vasoconstrictor response, however, is enhanced. The relative contribution of β-adrenergic stimulation and vagal withdrawal to cardioacceleration may vary with experimental conditions. Atropine has little or no effect on orthostatic tolerance.

The sympathetic activation is clearly nonuniform. Vasoconstriction is manifest before heart rate or con-

tractility is measurably affected. Forearm flow and conductance decrease significantly before splanchnic flow is affected (1, 167). The differential effects on limb flow and splanchnic flow are probably related to a predominance of low-pressure baroceptor effects at mild degrees of LBNP and increasing effects on the carotid sinus with progressive pooling and decreasing arterial pressures and pulse pressure (1, 167). Nonuniform regional vasoconstrictor responses may also be related to differential effects of changes in the impulse flow from ventricular and arterial baroceptors and to unequal levels of basal vasoconstrictor activity (350).

The baroceptor-mediated vasoconstriction in skin and muscle is apparent, although attenuated, even when opposed by thermoregulatory vasodilatory reflexes (166). Thus arterial and venous responses to a hot environment combine to increase the sensitivity to orthostatic stress. Conversely, cooling the skin attenuates the cardiovascular effects of LBNP (266, 267). The combined effects of a hot environment on resistance and capacitance vessels also impair ventricular filling during upright exercise (166, 279).

The involvement of multiple sets of the receptors may explain the relative lack of compensatory tachycardia when venous pooling has caused large decreases in stroke volume and cardiac output and falling arterial mean and pulse pressures. Presyncopal heart rates rarely exceed 130 beats/min; i.e., they remain at least 40 beats below normal maximal heart rate. This relatively slow rate may be the result of opposing chronotropic drives originating in the venoatrial and the cardiac and arterial receptors. This dissociation may

have a role in hypovolemic syncope. Furthermore a reduction of ventricular dimensions during the presyncopal state may progress until the end-systolic volume approaches zero and until endocardial deformation receptors are stimulated by compression during systole rather than by high wall tension, as in obstruction of the left ventricular outflow tract (222). Bradycardia and vasodilatation would then be produced by a Bezold-Jarisch-type reflex (92). Echocardiographic studies (5, 251, 292) support this mechanism by demonstrating a trend toward smaller end-systolic volumes with progressive venous pooling. The unstable autonomic state during presyncope with large oscillations in heart rate and arterial pressure (157) may reflect variations in the balance between opposing drives from atrial, ventricular, and arterial receptors.

CARDIOVASCULAR ADAPTATION TO PROLONGED
BED REST, ZERO GRAVITY, AND
RELATED CONDITIONS

Experimental Conditions

The human responses to prolonged exposure to zero gravity, bed rest, and water immersion have many important features in common. The hydrostatic intra- and extravascular pressure gradients that are normally present in the upright position are abolished or minimized. This causes a central or cephalad fluid shift that initiates a complex series of adaptive changes in several organ systems. After adaptation, reexposure to normal gravitational forces produces signs of orthostatic intolerance.

BED REST. More information is available on prolonged bed rest than on other hypogravic conditions. A recent summary (249) lists more than 500 American, European, and Russian bed-rest studies performed between 1921 and 1978. Early experiments concentrated on the metabolic effects of bed rest and immobilization and documented increased nitrogen excretion (54), calcium loss (6, 71), and decreased glucose tolerance (38). Clinically important side effects of bed rest, including loss of muscle mass and strength, cardiovascular deconditioning, and an increased risk of venous thromboembolism, were recognized during the early 1940s (75, 141, 203, 204). Taylor et al. (326, 327) and Dietrick et al. (74) described the principal effects on body-fluid distribution and cardiovascular function, i.e., decreased blood volume, orthostatic intolerance, and decreased exercise capacity in the upright position. The establishment of the US manned space-flight program in 1958 and extensive use of bed rest as a model of weightlessness yielded many studies during the 1960s.

HEAD-DOWN TILT. Russian investigators introduced bed rest with head-down (antiorthostatic) tilt, usually at −4° to −6°, as a more effective technique of simulating zero gravity than horizontal bed rest (177).

Several Russian and American studies (37, 65, 177, 180, 250, 302, 303, 343) have demonstrated that the effects of head-down tilt are qualitatively similar to those of bed rest except that the adaptation is accelerated. During short-term experiments head-down tilt produces a greater degree of cardiovascular deconditioning than horizontal bed rest of equal duration. One study (158) has failed to demonstrate any difference between the two modes. In general the comparisons of the effects of space flight and head-down tilt support the use of tilt as a simulation method for cardiovascular studies (37, 250, 291).

IMMERSION. The immediate effects of water immersion on fluid distribution and hemodynamic conditions are (as discussed in IMMERSION, p. 1030) more powerful than those of bed rest and head-down tilt. Prolonged immersion is logistically difficult, but hemodynamic measurements have been obtained over periods of several hours (4). Immersion periods of up to 56 days have been accomplished by protecting the subjects from water contact by wrapping them in thin plastic sheets (302).

ZERO GRAVITY. Only limited physiological data on the effects of zero gravity were collected during the early phases of the US and USSR manned space-flight programs (261). More extensive studies were made during the Apollo flights of 6–12 days (174), the three Skylab flights of 28–84 days (173), and the two Russian Salyut-6 flights of 96 and 140 days (359).

Data obtained during actual space flights are, of course, crucial in the study of the effects of gravity on the cardiovascular system, but the number of subjects that can be studied in space and the range of methods are, although rapidly expanding, still very limited. Ground-based simulation methods may closely reproduce many important aspects of weightlessness, but residual hydrostatic gradients are always present. The earth's gravitational field can be cancelled in aircrafts following parabolic or Keplerian flight patterns but only for periods of less than 45 s (291). However, there is no conclusive evidence that zero gravity has any unique or specific effects on the cardiovascular system that cannot be reproduced at least in kind during earthbound simulation studies. Similar considerations apply to the musculoskeletal system, but the effects of zero gravity on the vestibular system are probably specific. Motion sickness is common during the initial week of space flight (123). Provocative tests at normal gravity cannot predict susceptibility. Unusual movements and an altered relation between vestibular and visual inputs during space flight are thought to be major pathophysiological factors (123).

Age, sex, and physical fitness may affect the response to zero gravity, but no conclusive information is available. Astronauts and cosmonauts with few exceptions have been male, age 35–45, and physically fit. Most bed-rest studies have been performed in normal men in their twenties, but the NASA-Ames Research

Center has during the past few years conducted a series of studies in women, 20-35 yr old, which in general fail to reveal any significant sex differences (116, 130, 247). Convertino, Hung, and co-workers (66, 156) recently completed a 14-day bed-rest study in 50-yr-old men. The responses, including the degree of post-bed-rest cardiovascular deconditioning, were qualitatively and quantitatively similar to those of younger men. Corresponding findings have also been made during and after head-down tilt (F. A. Gaffney and C. G. Blomqvist, unpublished observations).

The role of physical fitness in the response to bed rest and related conditions is complex. Exercise has been used extensively to counteract deconditioning. Very fit subjects on the other hand appear to recover more slowly from prolonged bed rest than sedentary subjects if pre-bed-rest exercise performance is the basis for comparison (287). Previously fit, deconditioned individuals are nevertheless likely to outperform sedentary subjects. Athletes have often been considered more sensitive to short- and long-term orthostatic stress than sedentary subjects (187), but objective comparisons of athletes and nonathletes have variable results (47, 246, 310).

Body Composition

Bed rest, space flight, and water immersion initially decrease body weight 1-2 kg because of a loss of extracellular fluid. The magnitude of the initial weight loss closely corresponds to the cephalad fluid shift (37, 202, 250, 335, 336, 353).

There is a brief and transient phase of plasma volume expansion because of transfer of fluid from the extravascular compartment, but a decrease in plasma volume accounts for about one-third of the early weight loss (84, 129, 137, 226-228, 332). The fluid-related weight loss occurs within 3-4 days during bed rest (127, 340) and within 1-2 days during head-down

tilt and space flight (37, 150, 250, 261, 335, 336). The effect of water immersion is more rapid. A change of more than 1 kg has been recorded after a 6-h period of immersion (90).

The average total weight loss during flights of 28-84 days in the nine Skylab crew members was 3 kg, corresponding to 4% of total body weight (335, 336). Changes within the initial 3 days in space accounted for ~50% of the total loss (Fig. 10). Leach et al. (199) identified three components of the changes in total body mass: *1*) early obligatory water loss of about a liter as a consequence of a central fluid shift, *2*) gradual loss of muscle mass due to disuse atrophy, and *3*) variable change in the amount of body fat due to a caloric deficit. Early potassium losses were significant during the Apollo missions and may have contributed to the development of transient arrhythmias (20). Potassium loss with hypokalemia has also been observed during short-term simulation experiments (LBPP) in primates (239). Data from later flights, however, suggest that muscle atrophy and loss of body fat account for most observed overall losses of potassium, nitrogen, and protein (199, 200, 202); arrhythmias have not been a significant problem. A calcium loss is physiologically important but numerically represents only a small fraction of the total weight loss.

Disuse atrophy of skeletal muscle can cause secondary changes of cardiovascular function by affecting muscle tone, venous pooling, and the response to exercise. Disuse atrophy preferentially affects red fibers in general (42) and postural muscles, which contain a high proportion of red or slow-twitch fibers (288). The atrophy is reversible; muscle mass is restored relatively rapidly (~2 wk) after experimental immobilization, but postural muscles (e.g., soleus) may require 3-4 mo to regain full strength (42). Similar observations have been made in rats after space flight (60, 256, 325).

Loss of calcium is consistent in the response to bed rest and weightlessness. Prolonged bed rest has pro-

FIG. 10. Body-mass measurement of Skylab-3 scientist pilot at 0 *g* with spring-loaded oscillating system in which frequency of oscillation was proportional to mass. [From Thornton and Ord (336).]
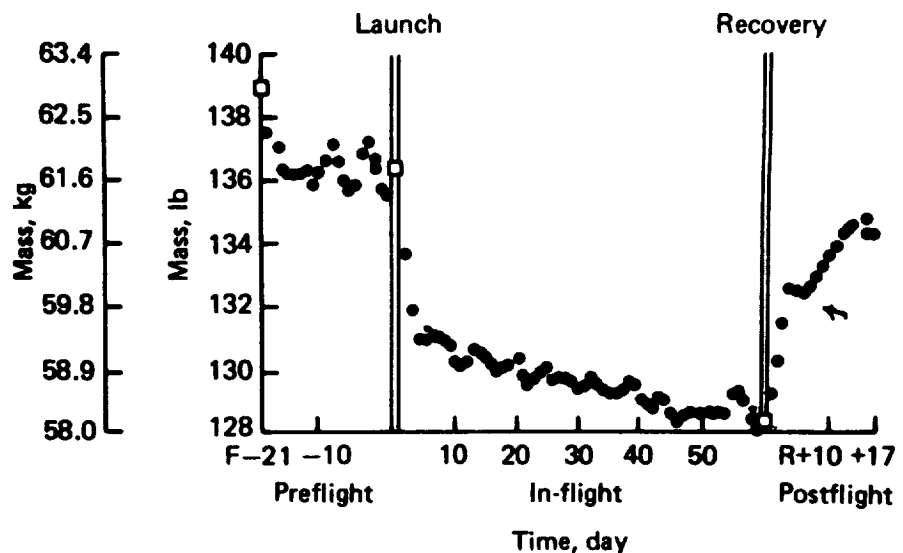
duced losses at a rate of 0.5% of total body calcium per month. The process is progressive, and the rate tends to accelerate (74, 77, 287). The calcium loss appears to be more severe during weightlessness than during bed rest. Balance studies during the Skylab flights demonstrated combined urinary and fecal losses at a rate as high as 2.5% of total body calcium per month (265). The threshold for clinically important osteoporosis is a cumulative loss of about 20%.

A balance between calcium uptake and loss is restored shortly after the return to normal gravity. Nevertheless prolonged exposure to weightlessness may cause irreversible skeletal damage. Urolithiasis is also a potential complication. Because it lacks effective countermeasures calcium loss is placed along with radiation exposure (337) as the other principal biological factor limiting the safe duration of space flight.

Calcium loss is almost certainly triggered by the absence or attenuation of the forces that normally support the body weight, i.e., compression forces acting on bone and shearing and tensile forces acting on periosteal surfaces. Bed-rest studies document failure of vigorous exercise in the supine position to prevent the calcium loss, whereas 3 h of quiet standing each day is effective (77, 164). Young patients immobilized with multiple fractures occasionally develop severe calcium loss from bone and secondary systemic manifestations of hypercalcemia, e.g., massive renal calcification with depressed function and hypertension. Dietary and pharmacological measures are ineffective (6, 64), but mobilization promptly normalizes calcium metabolism.

The exact cellular mechanisms mediating the calcium loss and the net absorption of bone during prolonged bed rest and space flight are unknown. Blood levels of calcium are usually only slightly elevated, and plasma levels of parathyroid hormone are low. No direct links to disturbances of cardiovascular function have been established.

Blood Volume

Plasma volume has been measured by similar techniques in many bed-rest studies, often by multiple determinations. The mass of red cells changes little during the initial 4 wk (127), and changes in plasma volume approximate the changes in total blood volume. The data from several studies with bed-rest periods of 6 h to 30 days (59, 126, 127, 170, 287, 314, 316, 338, 340–342) indicate significant plasma volume decreases within 6 h. The plasma volume contraction is progressive during the first 3 days, but then a plateau is reached at an average loss level of 350 ml or about 12%. Greenleaf et al. (126) performed a similar analysis of the literature and derived a nonlinear regression equation indicating a progressive loss through 60–80 days. Their estimate was heavily influenced by data from a single long-term study (77) with very large losses, 600–1,000 ml at a duration of 70–200

days. However, a similar long-term Russian study (258) showed a loss of 12% after 120 days, a value equal to the typical loss after 4–30 days.

A blood volume loss of 5%–15% is also a feature of space flight and head-down tilt. Prolonged space flight produces a combined loss of red cell mass and plasma volume. Data from early US flights demonstrated loss of red cell mass also after relatively short missions, but exposure to a hypobaric but hyperoxic atmosphere may have affected these results. A significant combined loss of plasma volume (−12.5%) and red cell mass (−11.1%) was observed after the normoxic Skylab flights and also after the 96- and 140-day Salyut-6 flights. The etiology of the decrease in red cell mass is not known, but the mechanism is bone marrow inhibition rather than increased destruction (171, 359). The interaction between the initial decrease in plasma volume and the effects on red cell mass during space flight and bed rest of very long duration need further exploration. The initial plasma volume loss with an increase in hematocrit and oxygen-carrying capacity may inhibit erythropoietin production (171).

Head-down tilt at moderate angles, −4° to −6°, and water immersion also cause blood volume losses of 350–500 ml. Most of these changes occur within 6 h (37, 108, 250). Immobilization in the upright position (i.e., chair rest), combined with horizontal bed rest during sleep, is associated with a reduction in plasma volume. The time course appears to differ from that during bed rest, however, implying a different mechanism. Lamb et al. (190, 192) found no significant changes after chair-rest periods of 4–8 days but a mean decrease of 376 ml after 10 days.

Cardiovascular Function

MAXIMAL OXYGEN UPTAKE. Maximal oxygen uptake as measured during a dynamic leg exercise is an important reference point in cardiovascular physiology. Pulmonary function does not limit uptake in normal subjects (except at high altitude); measurements of the maximal rate of oxygen uptake therefore estimate the overall functional capacity of the cardiovascular system. Cardiac pump function is probably the rate-limiting step under normal conditions, but peripheral mechanisms are likely to become important in many experimental situations. Thus, whereas measurements of maximal oxygen uptake accurately reflect changes in total cardiovascular performance, supplementary data are needed to isolate specific mechanisms.

In normal young men, bed rest of 3–4 wk decreases maximal oxygen uptake (measured during exercise in upright position) 13%–28% (31, 237, 287, 327). Similar changes (−15% after 10 days) have recently been reported in 50-yr-old men (66). Changes during exercise in the supine position in comparable groups are much smaller (66, 67, 112). Data on maximal oxygen uptake after space flight or immersion are not available. Nixon, Blomqvist, et al. (250) reported a decrease of

22% in normal young men after 24 h of head-down tilt at −5°. Lamb et al. (192) found no significant changes in maximal oxygen uptake after prolonged chair rest.

CARDIAC DIMENSIONS AND PERFORMANCE. Adaptation to hypogravic conditions reduces heart size. Saltin, Blomqvist, et al. (287) estimated a significant (−11%) decrease in total heart size in the supine position from biplane roentgenograms in young men after a 3-wk period of bed rest. Radiographic measurements after space flight have consistently demonstrated a decrease in heart size (248). Echocardiography before and after the Skylab-4 flight and two long Salyut-6 flights also showed a decrease in left ventricular end-diastolic diameter (148, 359).

Saltin, Blomqvist, et al. (287) noted that stroke volume was depressed in both the upright and supine positions after bed rest and postulated that prolonged bed rest depressed intrinsic myocardial function. They assumed that any abnormalities exclusively caused by decreased ventricular filling would be abolished in the supine position (25, 26). However, recent echocardiographic and scintigraphic studies have demonstrated decreased preload also in the supine position after adaptation and effectively ruled out any significant changes in contractile performance. Scintigraphic studies by Hung et al. (156) after bed rest showed an increased left ventricular ejection fraction at rest and during exercise both in the supine and upright position. Relative tachycardia was present during upright and supine exercise. The data, derived from a study of 50-yr-old men, indicate that an increased ejection fraction combines with relative tachycardia to compensate for the effects of the decreased end-diastolic left ventricular volume. Head-down tilt (37, 250) also decreases upright and supine stroke volume without changing the contractile state.

Henry et al. (148) found no change in intrinsic cardiac performance after prolonged space flight. They evaluated by echocardiography the ventricular function curves relating left ventricular stroke volume to end-diastolic volume. Two of the three subjects showed a small decrease in estimated left ventricular mass. Russian investigators have recently described ultrastructural myocardial abnormalities affecting the mitochondria and sarcoplasmic reticulum as well as capillaries and venules in rats exposed to zero gravity for 20 days (274). Furthermore the reduced left ventricular size in the Salyut-6 cosmonauts after return to normal gravity was associated with increased left atrial diameter, according to echocardiography (359).

The combined data on cardiac dimensions after bed rest and after space flight strongly suggest a reduction in filling pressures in the postadaptive state. Few direct pressure measurements have been made. Katkov et al. (180) reported no significant changes in supine right ventricular end-diastolic pressure after 5 days of head-down tilt at −4°, but Blomqvist et al. (37) recorded a significant decrease in central venous pressure (from 4.9 to 2.5 cmH₂O) after 24 h of head-

down tilt at −5°. Hemodynamic data (see SYSTEMIC HEMODYNAMICS, below) are also consistent with decreased filling pressures after adaptation. On the other hand the early stages of supine bed rest and head-down tilt (37) are probably associated with a transient increase in filling pressures above the levels prevailing in the upright position. Water immersion and head-down tilt raise filling pressures above the normal supine level.

There are no longitudinal data on filling pressures and cardiac output from bed-rest studies. Direct measurements during head-down tilt indicate that the increase in central venous pressure is transient and lasts less than 2 h, whereas the hemodynamic change during immersion persists for several hours with no signs of resolution (4, 37, 81, 250). Because no direct measurements are available the time course and magnitude of changes in filling pressures during space flight can only be guessed. Clinical observations indirectly support a sustained elevation of venous pressures, which may be associated with a hyperkinetic state. Distended neck veins, a puffy facies, and subjective sensations of fullness of the head are consistent features at zero gravity (186, 335). During the Skylab flights this condition persisted over periods of up to 84 days. Yegorov (359) reported a postflight increase in left atrial diameter, consistent with a sustained volume overload similar to conditions during immersion. Studies on supine cardiac dimensions immediately after return to normal gravity, however, clearly indicate an adaptation with decreased ventricular filling. Possibly the distension of the neck veins and the facial edema in space only reflect equilibration of systemic venous pressures. Regional differences in the compliance of the cutaneous vasculature and in tissue-filtration characteristics (186) may combine with an altered regional distribution of venous pressure to produce physical signs of venous congestion in the absence of any sustained elevation of cardiac filling pressures. The Skylab astronauts retained a normal capacity for heavy dynamic leg exercise in space (236); this is strong evidence against any major cardiovascular dysfunction at zero gravity.

Simulation studies provide no conclusive evidence for a sustained hyperkinetic state in space. The magnitude of the central fluid shift and the degree of postadaptive dysfunction are similar after space flight and head-down tilt. A sustained hyperkinetic state with an increase in filling pressures may be a unique product of the hydrostatic conditions that are associated with immersion, and the response to zero gravity may be better approximated by the adaptation to head-down tilt. Immersion causes tissue compression and a significant transthoracic pressure gradient, features that are absent at zero gravity and during head-down tilt.

SYSTEMIC HEMODYNAMICS. The principal effects on systemic hemodynamics of 3 wk of bed rest in normal young men are illustrated in Figure 11. The most
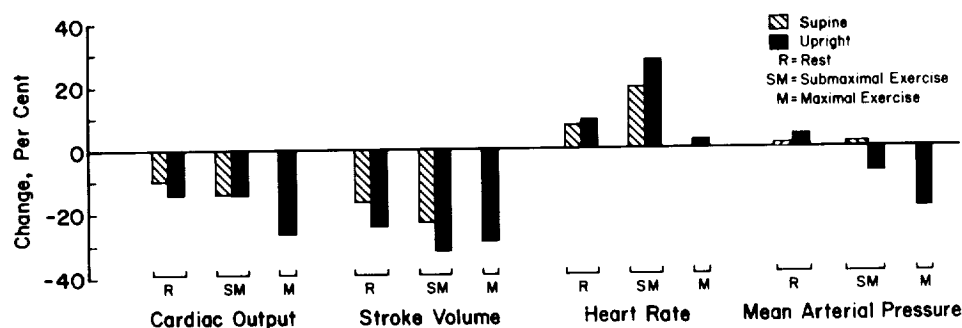
FIG. 11. Hemodynamic effects of 3-wk bed rest on cardiac output, stroke volume, heart rate, and mean arterial pressure supine and upright at rest during exercise in 5 normal young men. Control measurements before bed rest = 100%. [Data from Saltin, Blomqvist, et al. (287).]

important change was a marked reduction in stroke volume at rest and during exercise, particularly in the upright position but also in the supine position. After bed rest a relative tachycardia was noted at rest and during submaximal exercise, but cardiac output was still significantly reduced. Maximal heart rate did not change. The systemic arteriovenous oxygen difference was higher after bed rest at rest and during submaximal exercise but unchanged during maximal work. The maximal oxygen uptake decreased in direct proportion to stroke volume. Mean arterial pressure remained unchanged at rest and during submaximal exercise but was significantly lower at the maximal level. Systemic peripheral resistance was generally higher after bed rest, but the changes were small and nonsignificant.

Hyatt (157) studied a series of 16 subjects before and after a 2-wk bed-rest period. Results obtained at rest and during submaximal exercise in the supine position paralleled the findings by Saltin, Blomqvist, et al. (287). The stroke volume was significantly reduced also in the supine position, particularly during exercise (−20%) and passive head-up tilt. Birkhead et al. (31) have reported similar results. Chobanian et al. (59) also found a markedly reduced stroke volume (−50%) compared to measurements before bed rest during 70° head-up tilt. Nixon, Blomqvist, et al. (37, 250) reported similarly large changes after a 24-h period of head-down tilt at −5°. Stroke volume at rest supine decreased by 22%. Limited observations are available on cardiac output and stroke volume at rest and during exercise after prolonged space flight. Measurements based on the CO_2 rebreathing method were performed in the Skylab crew members after 28–84 days in space. Stroke volume during submaximal exercise decreased by more than 30% compared to preflight data (51, 236). Similar results were obtained after the 2- and 8-day flights of Soyuz 12 and 13 (181).

Extensive heart-rate data are also consistent with a significant stroke volume reduction at rest and during exercise after bed rest and related conditions. Post-bed-rest heart rates during relatively heavy submaximal exercise increased 30 beats/min in the upright and 25 beats/min in the supine position in the study by Saltin, Blomqvist, et al. (287). Others have reported

similar results after prolonged bed rest (31, 66, 157, 327), head-down tilt of short duration (37, 250), and space flight from 6 to 84 days (51, 236, 283). In contrast the in-flight exercise data from the Skylab missions (236) showed little or no change from preflight data. Three of the nine Skylab crew members actually had lower heart rates during exercise in space, suggesting, if anything, an improved exercise capacity at zero gravity.

There is little information on the distribution of cardiac output during and after exposure to hypogravic conditions. Saltin, Blomqvist, et al. (287) found a normal systemic arteriovenous oxygen difference during maximal exercise consistent with a normal pattern of redistribution of flow to active tissues.

Physical signs and symptoms suggesting cranial venous congestion at zero gravity have raised concerns about the state of the cerebral circulation. However, there is no evidence for any significant impairment of cerebral function in space. Russian studies on the cerebral circulation at zero gravity and during head-down tilt, based on direct measurements of arteriovenous oxygen differences (179) and rheography or impedance plethysmography (359), suggest increased cerebral flow, but the significance of these findings has not been established.

ORTHOSTATIC INTOLERANCE. Many bed-rest studies measuring heart rate and indirect arterial pressure have evaluated changes in orthostatic tolerance. Head-up tilt at 70° for 5–20 min is the most widely used method, but a variety of alternate procedures has also been employed, e.g., LBNP and $+G_z$ centrifugation. The maximal heart-rate difference between supine rest and head-up tilt typically increases from about +25 beats/min before bed rest to +40–+50 beats/min after bed rest (59, 194, 327, 340, 342). Arterial pressures during orthostatic stress are lower after prolonged bed rest, and the incidence of presyncope and syncope increases significantly. Brief exposure to head-down tilt (24 h) and to water immersion (6 h) has produced equally large changes in orthostatic tolerance, as judged from the heart-rate response to LBNP and tilt (37, 228, 250).

The Skylab-4 astronauts showed an average post-

flight increase in heart rate during LBNP at −50 mmHg of 27 beats/min after 89 days in space. In-flight LBNP measurements demonstrated similar changes. Decreased tolerance developed during the first few days without further changes, and toward the end of the flight there was even some improvement (172). The Apollo astronauts (150) had after much shorter exposure to zero gravity a mean heart rate during LBNP at −50 mmHg of 109 beats/min compared to 76 beats/min preflight, i.e., a difference of 33 beats/min.

Countermeasures. Investigators have tested a wide variety of interventions in attempts to prevent the cardiovascular deconditioning induced by bed rest and space flight. Principal approaches include exercise, redistribution of venous volume, and blood volume expansion.

1. Even vigorous exercise in the supine position fails to prevent orthostatic intolerance after bed rest. The effects on exercise capacity in the upright position are variable. A significant decrease is rarely prevented, but the reduction tends to be smaller than in nonexercising controls (29, 30, 45, 56, 194, 237, 323). Most investigators have used dynamic exercise, but static exercise had unexpectedly favorable effects in a study by Stremel et al. (323). Exercise may be a more valuable countermeasure during space flight than during bed rest. The crew members of Skylab 4 performed a large amount of exercise in space and had less cardiovascular dysfunction postflight than the crew members of Skylab 2 and 3, who exercised less vigorously during their shorter missions (172, 236). Current Russian in-flight regimens also include an extensive exercise program (359).

2. Intermittent redistribution of venous volume during bed rest to approximate the normal intravascular pattern during sitting or standing is helpful. Birkhead et al. (29, 30) demonstrated that a daily 3-h standing or 8-h quiet sitting prevented the development of orthostatic intolerance. Prolonged application of LBNP is cumbersome but prevents or minimizes plasma volume loss and orthostatic intolerance (191, 314–316). Other devices, designed to simulate normal hydrostatic gradients, e.g., an elastic reverse-gradient garment, have been effective in short-term (<4 h daily) applications (67). Currently LBNP devices with relatively few restrictions on body movement in space are being evaluated in both the Russian and American space programs.

3. Reexpansion of the blood volume to pre–bed-rest levels has been achieved by oral administration of 9α-fluorohydrocortisone during the last 3 days of a period of prolonged bed rest, but orthostatic intolerance persisted (313, 317). Hyatt (157) administered daily doses during a 10-day bed-rest study and produced a blood volume expansion relative to control values before bed rest. The heart rate during post–bed-rest tilt nevertheless remained slightly elevated. Later rehydration experiments by Hyatt and West (159) tested the effects

of oral administration of saline at the end of a 1-wk bed-rest period. Saline alone did not restore plasma volume and orthostatic tolerance, but the combination of saline and a 4-h period of LBNP produced a transient return to pre–bed-rest levels. In a recent study after a 24-h period of head-down tilt at −5° (37), intravenous saline infusion sufficient to bring central venous pressure back to pretilt levels in the supine position failed to restore orthostatic tolerance but essentially abolished the loss of exercise capacity in the upright position. Normalization of central venous pressure required a volume corresponding to twice the blood volume loss.

4. Other countermeasures, including exposure to simulated high altitude (317) and mechanical devices designed to introduce sudden large longitudinal *g* forces (56), have generally been ineffective. Three recent approaches have provided intriguing but as yet unconfirmed results. Bhattacharya et al. (27) found that whole-body oscillation (half-sine function at 1 Hz for 20 min daily) prevented orthostatic intolerance after immersion. Prophylactic treatments with a β-adrenergic blocking agent (233) and a calcium antagonist (39) have also been used successfully in small groups of subjects.

Mechanisms. Postural hypotension, i.e., an abnormally low arterial pressure in the upright position, is a common clinical problem. Some aspects of the pathophysiology provide relevant background material for the analysis of the orthostatic intolerance after bed rest and related conditions. There are two principal primary mechanisms: *1*) an abnormal degree of orthostatic central hypovolemia and *2*) inadequate cardiovascular regulatory responses. The regulatory and hemodynamic patterns in the hypovolemic group exaggerate the normal response, i.e., increased adrenergic drive reflected by elevated plasma catecholamines, marked tachycardia, and vasoconstriction. The second group is heterogeneous and includes conditions that abolish or attenuate the cardiovascular responses to physiological redistribution of hydrostatic pressure gradients and intravascular volumes.

1. Hypovolemic hyperadrenergic postural hypotension [arterial circulatory anemia (33) and sympathicotonic orthostatic hypotension (253)] is caused by a reduction in total blood volume or an abnormal volume distribution during orthostatic stress. Variations in total blood volume well within the physiological range affect orthostatic tolerance. Murray et al. (241) examined the combined effects of venesection and LBNP. Measurable orthostatic intolerance appeared after an acute blood volume loss of 500 ml. Bergenwald et al. (19) studied normal subjects during prolonged head-up tilt and found that fainters had significantly lower (−8%) total blood volume than nonfainters. The size of the central blood volume pool may also be an important determinant. Women have larger increases in heart rate and decreases in arterial pressure and stroke volume than men at a given degree of venous

pooling and also a smaller basal end-diastolic ventricular volume and a limited systolic reserve (101, 292).

Gaffney, Blomqvist, et al. (100, 102) have studied patients with mitral valve prolapse and hyperadrenergic postural hypotension. The functional characteristics of the abnormal valve probably contribute to the orthostatic intolerance by causing an abnormally large decrease in stroke volume in the upright position although these patients also have an inappropriately large increase in vasoconstrictor activity in the upright position and a significantly reduced total blood volume. The combination of a chronically vasoconstricted state, hypovolemia, and postural hypotension is also present in some patients with essential hypertension or pheochromocytoma.

Conditions that increase peripheral venous pooling are associated with orthostatic intolerance. Patients with massive venous varicosities or a congenital absence of the venous valves have postural hypotension and decreased exercise capacity in the upright position (26). They also have an increased compliance of nonvaricose veins (363). The most important physiological mechanisms affecting the degree of pooling are linked to thermoregulation. Venous compliance and pooling are proportional to skin temperature. Heat significantly reduces and cold increases orthostatic tolerance (145, 147, 266, 267).

2. Normovolemic regulatory postural hypotension [postural (44), orthostatic (33), and asympathicotonic (253) hypotension] can be caused by 1) abnormal baroceptor function, 2) peripheral or central lesions of the nervous system interrupting afferent or efferent neural pathways or causing dysfunction of the medullary cardiovascular control centers, or 3) end-organ failure to respond to autonomic stimuli. Such failure may be caused by nonneural lesions, e.g., lack of postural heart-rate response in patients with a degenerative disease of the sinus node (sick-sinus syndrome) or complete heart block. High- and low-pressure baroceptor function is altered in many different cardiovascular disorders (2, 76, 82), but the efferent rather than the afferent limb is usually involved in patients with severe orthostatic hypotension. The response pattern is hypoadrenergic, with a lack of tachycardia and vasoconstriction. Parasympathetic involvement may also be a factor. Autonomic dysfunction with hypoadrenergic orthostatic hypotension may be idiopathic or one of several clinical manifestations of many different systemic and neurological disorders, e.g., diabetic neuropathy, tabes dorsalis, amyloid diseases, syringomyelia, traumatic lesions of the spinal cord, cerebrovascular disease, tumors, and degenerative or demyelinating diseases of the central nervous system (21, 25, 160–162, 212, 297, 298, 344).

Idiopathic orthostatic hypotension and the Shy-Drager syndrome are relatively rare forms. They are diseases of late middle age with general signs of dysfunction of the autonomic nervous system, e.g., bowel and bladder disturbances, inability to sweat, and im-

potence. The Shy-Drager syndrome (304) identifies a distinct group of patients who have orthostatic hypotension and signs of extrapyramidal tract involvement (Parkinson's disease); there are widespread but nonspecific degenerative lesions of the central nervous system. Patients with the Shy-Drager syndrome or idiopathic orthostatic hypotension often have abnormal cardiovascular function also at rest supine. The functional characteristics of the heart suggest denervation. Stroke volume is low, perhaps because of a decreased contractility, and there is mild tachycardia at a relatively fixed rate. Peripheral resistance increases rest, but the postural vasoconstrictor responses are absent or greatly attenuated (161, 162). Humoral abnormalities can also be demonstrated. The catecholamine response to orthostatic stress is attenuated or absent (263, 361), and postural changes in plasma renin levels are often but not always (43, 212) subnormal, consistent with an efferent autonomic block. Some patients also have diminished aldosterone responses and a decreased ability to conserve sodium (142).

The hypovolemic-hyperadrenergic and the normovolemic-hypoadrenergic varieties of postural hypotension cannot always be clearly distinguished. Ibrahim et al. (160–162) have shown that patients with idiopathic orthostatic hypotension have a reduced blood volume and vasoconstriction at rest supine with increased arterial pressure and total peripheral resistance.

Orthostatic tolerance is often increased in certain clinical conditions, e.g., hypertension and congestive heart failure (3, 243, 298). Cardiac performance characteristics with attenuated preload effects on the stroke volume, decreased venous compliance, and increased total and central blood volumes together counteract autonomic dysfunction with blunted reflex responses (76, 79, 82).

Orthostatic intolerance after prolonged bed rest and related conditions. A critical analysis of the descriptive material that has been presented on the effects of prolonged bed rest and related conditions and on countermeasures identifies the following salient points:

1. Prolonged bed rest (horizontal, with head-down tilt), water immersion, and exposure to zero gravity produce actual and functional hypovolemia.

2. Postintervention cardiovascular dysfunction is characterized by orthostatic intolerance and decreased exercise capacity. Left ventricular end-diastolic volume and stroke volume are reduced in both the upright and supine positions. Intrinsic myocardial function is not depressed.

3. The degree of cardiovascular dysfunction is more severe than expected from the magnitude of the blood volume loss. Volume for volume replacement significantly improves hemodynamics but does not fully restore normal function.

4. The altered distribution of body fluids with a

headward shift is probably more important than inactivity in the development of cardiovascular dysfunction. Intermittent redistribution of venous volume (LBNP, short periods of standing) to match the conditions that normally prevail in the upright position protects against orthostatic intolerance. Vigorous exercise is less effective. Furthermore the cardiovascular dysfunction induced by prolonged bed rest or space flight is similar to that induced by periods of water immersion or head-down tilt of 24 h or less. Adaptation to inactivity, as reflected by functional and structural changes in the musculoskeletal system and the myocardium, is slower.

The discrepancy between the magnitude of the blood volume loss and the severity of the cardiovascular dysfunction suggests that adaptation produces changes in venous function, e.g., increased compliance, an abnormal pattern of postural redistribution of blood volume, systemic regulatory abnormalities, or a combination of these features. The increased heart-rate response to orthostatic stress after exposure to hypogravic conditions is consistent with a hypovolemic-hyperadrenergic pattern. However, there is only inconclusive evidence for a postadaptive increase in venous compliance and the degree of venous pooling needed to amplify the effects of the modest decrease in blood volume. Immersion produces an increase in peripheral venous compliance that persists for the duration of the intervention (81). Stevens et al. (316) found an increased venous compliance after bed rest reflected by measurements of leg volume changes during LBNP. Occlusion plethysmography during and after the Skylab-4 flight suggested increased venous compliance, whereas measurements of leg volume changes during LBNP showed increased pooling only at zero gravity (335). On the other hand estimates of the compliance of the arm (occlusion plethysmography), the leg (leg volume changes during LBNP), and the systemic veins (relating central venous pressure to leg volume changes during LBNP) showed no changes after adaptation to head-down tilt (37). Thornton et al. (335) suggested that decreased skeletal muscle tone contributes to an increased degree of venous pooling after space flight and bed rest.

Data on autonomic function after bed rest and space flight are inconclusive. As discussed earlier in this section, the postadaptive heart-rate response to orthostatic stress is increased, which may be an appropriate compensation for a decrease in stroke volume. The normal vasoconstrictor responses also appear to be intact (37). Chobanian et al. (59) found no bed-rest–induced changes in the pressor responses to norepinephrine and angiotensin infusions. Plasma catecholamines were reduced during bed rest, but the response to tilt was unchanged. The apparent turnover rate of norepinephrine was also normal. However, Schmid et al. (294) demonstrated decreased vaso- and venoconstrictor responses to intra-arterial tyramine after a 12-day bed-rest period. The responses to nor-

epinephrine did not change. These findings are consistent with normal receptor function but impaired release of endogenous norepinephrine, perhaps caused by a decreased rate of synthesis. Furthermore Billman, Dickey, Stone, and associates (28, 73) have recently documented reduced baroceptor sensitivity and altered responses to vasoactive drugs after long-term horizontal immobilization in rhesus monkeys.

The combined data, although incomplete and inconclusive, suggest that the orthostatic intolerance after bed rest and related conditions is a multifactorial disorder. Changes in effective venous compliance and perhaps also subtle autonomic dysfunction appear to amplify the effects of a moderate absolute hypovolemia.

Dynamic Responses

Most studies of prolonged bed rest and related conditions have been limited to static before-and-after comparisons, and little is known of the dynamic response. Nevertheless there is strong evidence that the primary stimulus for the adaptation is the shift of intravascular and interstitial fluid from the lower to the upper half of the body, particularly to the central circulation. The absolute magnitude and exact time course of the responses to bed rest, head-down tilt, immersion, and weightlessness vary for specific functions, but enough similarities have been documented to justify the use of head-down tilt as a tentative model for analysis of the general features of adaptation to hypogravic conditions.

Figure 12 is based on two experiments with 24-h head-down tilt at $-5°$, each including five normal young men (37, 250). The base line for all measurements was supine rest. A decrease in leg volume of
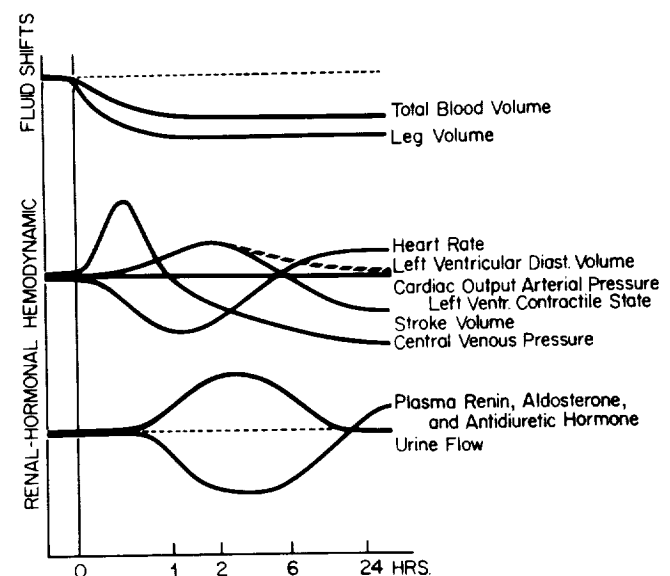

FIG. 12. Diagram of early adaptation to simulated $0\,g$ (head-down tilt, $-5°$). [From Blomqvist et al. (37).]

about 1 liter during the initial 2 h indicates a central fluid shift. Central venous pressure increased significantly by 2.5 cmH_2O but returned to the base line within 1 h. This decrease was associated with a transient apparent increase in venous compliance, whereas effective systemic and peripheral venous compliances were normal at the end of 24 h. Stroke volume and left ventricular end-diastolic volume also increased transiently and reached a maximum somewhat later than central venous pressure, or at about 2 h. The contractile state did not change, nor did cardiac output. The increase in stroke volume was offset by relative bradycardia. Arterial pressures also remained unchanged. Central venous pressure and stroke volume were at 24 h below the base line, and the heart rate was slightly elevated.

Plasma renin, aldosterone, and ADH levels decreased transiently during the initial 6 h and a diuresis produced a weight loss equal to the loss in leg volume and more importantly decreased total blood volume 350 ml. Neither plasma osmolality nor electrolyte concentrations changed, but the urinary sodium/potassium excretion ratio increased.

Gauer and Henry (107) considered activation of low-pressure baroceptors, reflex inhibition of ADH, and a water diuresis as the primary responses to a central fluid overload. The discrete venoatrial receptors are probably important (209), but impulses originating in the atrial and ventricular C fibers may also have a significant impact on renal function and the fluid-electrolyte balance (334). The role of atrial distension has been disputed (115). Epstein et al. (87, 89, 90) have clearly documented inhibition of the renin-aldosterone system and a saluresis during immersion experiments. Their data also indicate that it is unlikely that osmoreceptors or changes in renal hemodynamics have a major role. Data on fluid balance and hormonal responses at zero gravity (200) differ from the results obtained during head-down tilt and immersion. No demonstrable diuresis coincided with the early weight loss during the Skylab flights, but fluid intake decreased. Data on the early hormonal responses in space are not available. Measurements during the early recovery phase after the Skylab flight (200) and after a study on head-down tilt by Volicer et al. (343) were consistent with a relative combined inhibition of ADH and aldosterone during exposure to hypogravic conditions and a reactivation during the recovery phase. The role of other hormones (prostaglandins, natriuretic hormone) is doubtful (87).

The apparent overshoot of the hemodynamic adaptation at 24 h with a reduced filling pressure and stroke volume relative to base-line levels in the supine position supports Gauer's thesis that the upright position is the normal operating condition. When the adaptation to the hypogravic state (i.e., bed rest, head-down tilt, or space flight) is complete, hemodynamic conditions approach those that normally prevail during sitting or standing. A system adapted in this fash-

ion has little reserve capacity to manage additional stresses caused by postural fluid redistribution. The cardiovascular dysfunction after bed rest and space flight therefore results from a successful adaptation that has suddenly been rendered inappropriate by the reexposure to normal gravitational fields and to large hydrostatic gradients.

HYPERGRAVIC CONDITIONS

Experimental Conditions

Hypergravic conditions can be generated within the earth's gravitational field by acceleration (i.e., changing velocity or direction of motion of a body). Linear acceleration occurs when the rate of motion increases or decreases without changing direction, and angular acceleration occurs when the direction of motion changes. For example, a car that is gaining or losing speed traveling down a straight road exposes the passenger to linear acceleration, whereas going around a curve creates angular acceleration. The terms *gravitational force* and *acceleration* are interchangeable because the physical quantity of gravity is defined as an acceleration. The acceleration of a body falling freely toward the earth's surface in airless space is 1 g, or 981 cm/s^2. It is correct to speak of a gravitational force (F) as the product of the mass of an object (m) and acceleration (a), or $F = ma$, if the mass is a constant. Mass then becomes a proportionality factor. In biomedical applications the mass of the object being studied, either a human subject or an experimental animal, does not change significantly over the course of an experiment.

A standard nomenclature has been developed that defines the anatomical direction of the gravitational force (Fig. 13). The two gravitational forces shown in Figure 13 act either through the long axis of the body ($\pm G_z$) or across the body from back to front or front to back ($\pm G_x$). A third gravitational force, not shown in Figure 13, acts across the lateral aspect of the body ($\pm G_y$). In general the gravitational force is expressed in multiples of unity. A force of 3 $+G_z$ is 3 times the normal gravitational force acting in the head-to-foot direction. In the following discussion the major emphasis is placed on gravitational forces acting in the $+G_z$ direction over periods of several seconds to minutes. Such forces may be viewed as an exaggeration of the forces acting during a change in body position from supine to upright. Gravitational forces of short duration (impact forces), i.e., 1 s or less, are not considered, and little information is available on the circulatory changes with $-G_z$ and $\pm G_y$ accelerations.

Hydrostatic pressure is a linear function of the force of gravity. Tripling the gravitational force triples the hydrostatic component of pressure along any fluid column parallel to the gravitational force. Hydrostatic pressure changes ~1 cmH_2O/cm vertical distance at 1

$- G_z$
negative G

FIG. 13. Standard reference system (direction and nomenclature) for gravitational forces acting on a subject through long axis of body ($\pm$ G_z), through sternum to backbone ($\pm$ G_x), and through lateral aspect ($\pm$ G_y, not shown).

$+G_x$
+Transverse G

$-G_x$
−Transverse G

$+G_z$
positive G
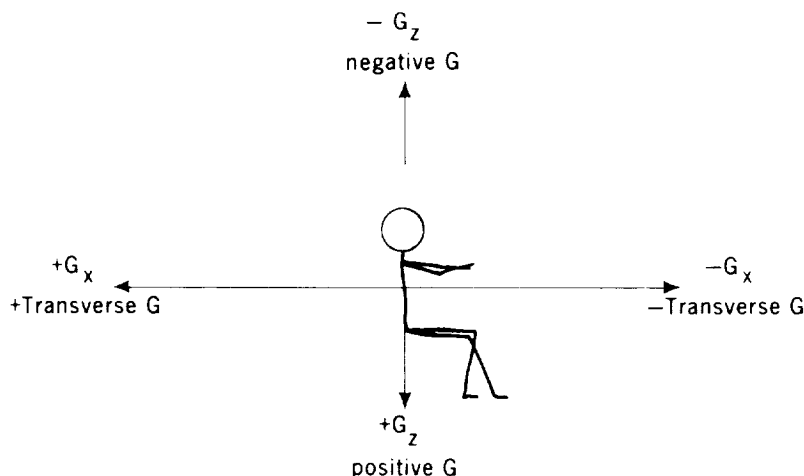
g. At 3 $+G_z$ the corresponding hydrostatic pressure change is 3 cmH_2O/cm vertical distance. In a fluid column exposed to an increased gravitational force, the local pressure at any site along the column varies directly with the position in the column either above or below the HIP.

Fluid Shifts

A $+G_z$ increase accentuates orthostatic fluid shifts from the intrathoracic compartment to the legs. Early work (104) in Germany on human volunteers demonstrated a large increase in the volume of the lower leg at 6–8 $+G_z$. Chest X-ray films taken during aircraft flight and centrifuge experiments indicated that the lung fields became clearer during increasing acceleration, which is consistent with a decrease in pulmonary blood volume or a redistribution of pulmonary blood flow. A loss of plasma volume to the interstitial space also accompanies the redistribution of blood volume. The amount of plasma volume loss depends on the duration and magnitude of the gravitational force (62, 132). Large volumes may be lost very rapidly at high G forces, e.g., 216–270 ml at 3.5–5.0 $+G_z$ maintained for 3–5 min.

The human regulatory responses to $+G_z$ acceleration have many features in common with the changes during standing. The shift of blood out of the thorax leads to an increase in plasma ADH levels (127, 183, 273). Plasma renin activity did not change with the increased gravitational force in these experiments, perhaps because of a large increase in plasma ADH or simply the short duration of the $+G_z$ exposure. Plasma renin activity increases in volunteers exposed to $+G_x$ acceleration for up to 30 min (91, 272). The increase in plasma ADH, not a result of a change in plasma osmolarity, probably is caused by the shift in blood volume and decreased activation of cardiopulmonary receptors (107, 108). In human volunteers $+G_z$ also causes a central blood volume shift that is associated with a reduction in plasma ADH and a diuresis (273). Exposure to high G forces, however, also produces

mechanical effects that may modify the regulatory responses.

Cardiac Dimensions and Performance

The heart is normally suspended by the central vasculature and the pericardium, which tends to make the heart vulnerable to increased gravitational forces, particularly to $+G_z$ acceleration. Gauer (104) initiated radiographic studies of the response to hypergravic conditions in cats and monkeys in 1936. Centrifuge experiments showed that $+G_z$ acceleration pushed the heart caudally and reduced both systolic and diastolic volumes. The apical portions of the ventricles were devoid of contrast material during systole. Contrast material was injected intravenously prior to the acceleration exposure, and no distinction could be made between the right and left sides. The obliteration of the apical cardiac chambers during $+G_z$ acceleration led to the hypothesis that the endocardial walls may actually rub against each other during systole, causing cardiac damage (111).

The end-systolic volume of the ventricles depends on the level of autonomic nervous system activity (contractile state) and the pressure in the aorta during ejection (afterload). The level of $+G_z$ acceleration greatly influences direct mechanical effects, the autonomic activity, and the aortic pressure. Erickson, Sandler, and Stone (93) studied anesthetized dogs during $+G_z$ acceleration and also demonstrated that the heart was progressively shifted caudally as the level of $+G_z$ acceleration was increased. In recent studies with similar conditions H. Sandler (unpublished observations) obtained cineangiograms from anesthetized dogs during $+G_z$ acceleration. Left ventricular diastolic and systolic volumes were reduced, but there was no evidence that the walls of the left ventricle actively hit each other during systole. The aorta and vessels leaving the arch of the aorta are stretched during $+G_z$ acceleration, and the diameter of the vessels is reduced. The coronary vessels apparently are not involved, and mechanical obstruction

during $+G_z$ acceleration is unlikely (93). During transverse acceleration $(+G_x)$ the heart is displaced toward the posterior portion of the thorax with minor changes in ventricular chamber dimensions (290).

The electrical activity of the human heart during acceleration stresses has been studied extensively for more than 35 years in both centrifuge and aircraft experiments. Gauer (104) described flattening of the T waves in the limb leads, sometimes associated with S-T segment elevation at higher acceleration levels. Cardiac dysrhythmias ranging from atrioventricular block to premature ventricular contractions were also seen. Gauer noted the similarity between these changes and those during myocardial ischemia and suggested that coronary flow was compromised during acceleration stress. In a subsequent study Zuidema et al. (364) found potentially serious cardiac arrhythmias in four subjects, one of whom also had chest pain. These findings may support the view that myocardial ischemia limits the ability of humans to tolerate $+G_z$ acceleration. However, acceleration levels as high as 9 $+G_z$ (50, 63, 114, 153, 300) have failed to produce any significant arrhythmias persisting after deceleration. In several studies premature ventricular contractions and multiform arrhythmias were observed during the early portion of the various acceleration profiles, but they disappeared either before or at the termination of the acceleration stress. This time course is inconsistent with ischemia. The movement of the heart in the chest cavity and increased efferent cardiac sympathetic activity could explain the electrocardiographic (ECG) changes in normal volunteer subjects. β-Adrenergic blockade prevents the T-wave changes induced by acceleration (63).

Blood flow to the myocardium during $+G_z$ acceleration has been examined in experimental animals (58, 93, 198, 300, 320), but the results are inconclusive. Chimoskey (58) found a decrease in coronary flow when unanesthetized dogs were exposed to brief durations (10 s) of $+G_z$ acceleration. The decrease in coronary flow coincided with the development of T-wave changes of the ECG. Shubrooks (300) found that coronary flow increased up to 3.5 $+G_z$ in anesthetized dogs during the early portion of the acceleration stress and either remained elevated or returned to control levels by the end of the 60-s stress period, whereas Erickson, Sandler, and Stone (93) found a decreased coronary flow in anesthetized dogs exposed to up to 4 $+G_z$. As coronary flow decreased so did coronary sinus oxygen saturation. This study would suggest some potential for myocardial ischemia. Using unanesthetized miniature swine, Stone et al. (320) found that coronary flow decreased up to levels of 9 $+G_z$ with the most significant decreases above 5 $+G_z$. Using microspheres to measure coronary flow and distribution in miniature swine, Laughlin et al. (198) found that coronary flow increased up to 7 $+G_z$. They used aortic pressure as a reference point for the measurement of coronary flow, however, and made no measurements

if the pressure fell below 100 mmHg. This and other variations in methodology may at least partially explain the divergent results of the flow measurements.

Flow measurements cannot provide information on the potential for ischemia without data relating to myocardial oxygen demand. The effect of $+G_z$ acceleration on the oxygen demand of the heart and on the balance between oxygen demand and supply is uncertain. Demand probably increases because of the increase in heart rate with maintenance or elevation of aortic root pressure, but the effect on wall tension is modified by a changing cardiac chamber geometry and probably also by changes in the contractile state.

Ultrastructural and biochemical changes have been observed in hearts taken from miniature swine immediately after exposure to various levels of $+G_z$ acceleration. Burton and MacKenzie (52) found left ventricular subendocardial hemorrhage that was directly related to the level and duration of acceleration exposure. Heart rate and/or the sympathetic nervous system were involved because β-adrenergic blockade reduced heart rate during acceleration and reduced the degree of subendocardial hemorrhage. In the same animals MacKenzie et al. (215) studied the ultrastructural changes and found myofibrillar degeneration, pooling of mitochondria, and involvement of the Purkinje fibers. Lindsey, Stone, et al. (210) also examined the ultrastructural changes of myocytes from swine exposed to 9 $+G_z$. They found changes similar to those described by MacKenzie et al. (215) and also evidence of disruption of contractile fibers in some cells. Biochemical studies (78) have demonstrated an increase in proteolytic enzyme activity in the myocardial cells up to 2 wk after acceleration exposure. Whether these signs of myocardial damage are caused by ischemia, hypoxia, or increased release of catecholamines is not known. How significant these findings are to potential hazards of acceleration stress $(+G_z)$ to humans is uncertain, but they should not be ignored.

Cardiac Output and Regional Flow

The ability of the cardiovascular system to withstand $+G_z$ acceleration is defined clinically by the appearance of limiting symptoms. The usual endpoint criteria for measuring acceleration tolerance progress from the loss of vision to unconsciousness. Loss of vision usually occurs around 4.0 $+G_z$ and blackout occurs around 4.5 $+G_z$ in relaxed humans (153). These endpoints vary considerably between and within individuals, and the threshold level can be altered by protective devices (anti-G suit) or maneuvers (straining). Lambert and Wood (193) measured eye-level arterial pressure in volunteers and found that vision was lost at an average arterial pressure of 20 mmHg. Figure 14 is a representative graph of the acceleration tolerance for $+G_z$. Levels of acceleration and times of exposure below the curve can be well tolerated by most relaxed humans.

FIG. 14. A representative average curve for $+G_z$ acceleration tolerance in relaxed humans in seated position. Top of graph, reported symptoms at these acceleration levels. Increased tolerance above 10 s is probably circulatory reflex compensating for increased gravitational force.
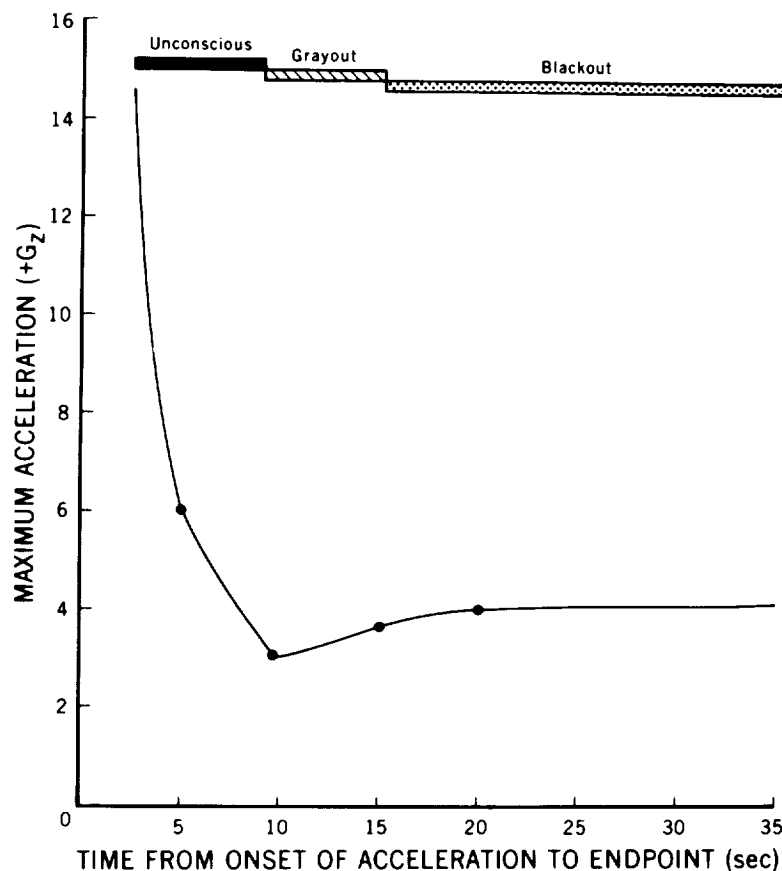
Shubrooks (300) found that heart rate increased in an almost linear fashion with increasing $+G_z$ acceleration up to levels of ~6 $+G_z$ in subjects protected from the usual endpoints of acceleration stress. Maximal heart-rate responses were achieved within 3–12 s after the occurrence of peak G levels, and rates tended to remain at this level for the duration of the experiment. Peak heart rates measured in this study ranged from 155 to 205 beats/min and were not related to the preacceleration heart-rate level. When the acceleration is terminated a considerable bradycardia usually ensues. The increase in heart rate in human subjects during $+G_z$ acceleration appears to be mediated mainly by the sympathetic nervous system with a minor contribution from vagal withdrawal (34, 35). The relative importance of sympathetic and parasympathetic mechanisms, however, is likely to vary with preexisting or background levels of autonomic activity (270). Upon cessation of the acceleration stress atropine can block the bradycardia (205), which clearly indicates a strong reversal of the autonomic nervous system balance occurring at the sinoatrial node. During $+G_x$ acceleration the heart rate also increases but less than during $+G_z$ acceleration. During $-G_z$ acceleration the heart rate decreases as the pressure rises in the region of the head and the carotid sinus.

Cardiac output and stroke volume have been measured in human volunteers during $+G_z$ acceleration

(207, 208, 275, 357). Table 3 shows representative results. Both cardiac output and stroke volume fall progressively with increasing gravitational force, but the aortic pressure measured at the heart level actually increases, indicating peripheral vascular adjustments during this type of stress. The decrease in cardiac output is the result of the peripheral shift in blood volume, a decreased venous return, and a reduced end-diastolic volume of the ventricles. Rosenhamer (275) found that cardiac output at 3 $+G_z$ remains about 3 liters/min below the expected levels at 1 $+G_z$ also during exercise. However, the rate of increase in cardiac output relative to oxygen uptake is similar at 1 and 3 $+G_z$, or about 6 liters/min for a 1 liter/min increase in O_2 uptake. Stroke volume also remains subnormal during exercise at 3 $+G_z$, but the increase on transition from rest to exercise is larger than at 1 $+G_z$.

Cardiac output in the human does not decrease during $+G_x$ acceleration (Table 3). Results were similar during moderate levels of $+G_x$ acceleration in experimental animals. Arterial pressure referenced to heart level was maintained and even increased slightly. There was a small decrease in stroke volume. A decrease in cardiac output was recorded at 15 $+G_x$ (318). Exceedingly high levels of $+G_x$ acceleration probably compromise ventricular filling when the heart is being pushed against the posterior chest wall.

PULMONARY BLOOD FLOW. The effect of 1 $+G_z$ on the regional distribution of pulmonary blood flow is well documented, and an increase in $+G_z$ acceleration is expected to accentuate it (352). Blood flow in the lungs shifts from the superior region of the lungs (apex) toward the more dependent lung region (base). This might cause greater right-to-left shunting of blood, which would reduce the oxygen content of arterial blood. Decreases in arterial oxygen saturation have been demonstrated in both humans and experimental animals exposed to acceleration stress (13-15, 252, 268, 312, 356). The decline in arterial oxygen content is progressive during $+G_z$ acceleration and can lead to saturation values less than 80% at 5 $+G_z$ (356). Oxygen breathing reduces but does not abolish the decline in oxygen saturation (14). The effective alveolar-arterial oxygen difference decreases on the transition from rest to exercise at normal gravity but increases during exercise at 3 $+G_z$, presumably because of an increase in the number of alveoli with low ventilation/perfusion ratios (275). During $+G_x$ acceleration arterial oxygen saturation at rest can decline to as low as 75% at 8 $+G_x$ (312). The increase in accelerative forces increases alveolar size in superior lung regions and decreases it in the dependent regions, causing a greater ventilation/perfusion mismatch (57, 131, 339).

BRAIN. The distribution of cardiac output has been examined to a limited extent in human volunteers and in experimental animals. As mentioned previously, loss of vision and unconsciousness are experimental endpoints for the termination of $+G_z$ acceleration. Clearly blood flow to the head must be reduced, since arterial pressure at eye level can fall below the range of cerebral blood flow autoregulation (149, 193). Total perfusion of the brain measured by the radioisotope-clearance technique was reduced at 2, 3, and 4 $+G_z$ in humans. The long time required to accomplish these measurements precluded studies at higher levels of acceleration (155) and also raises some questions concerning the measurements at 2-4 $+G_z$, since a steady-state condition is a prerequisite for accurate measurement. In anesthetized primates, cerebral blood flow remained almost constant until arterial pressure at the base of the brain dropped below 65 mmHg at which point cerebral flow declined as arterial pressure fell (H. L. Stone, unpublished observations). This occurred at 3.0-3.5 $+G_z$ in all animals studied. Clearly there is no way to relate this level to loss of vision in these anesthetized animals, but the decreasing pressures strongly suggest a reduction in blood flow to the brain. Cerebral blood flow has not been measured during $-G_z$ acceleration, but there is no reason to suspect that it is compromised.

SPLANCHNIC AND MUSCLE BLOOD FLOW. Howard and Garrow (154) and Stone (318) measured forearm blood flow, splanchnic blood flow, and arterial pressure in six normal volunteers (Fig. 15). Forearm blood flow, measured by a mercury-in-Silastic strain gauge, de-

creased considerably at 3 $+G_z$ compared to 1 g. Resistance increased, indicating active vasoconstriction. Splanchnic blood flow (indocyanine-green clearance) changed little, and the pressure-flow ratio increased, suggesting splanchnic vasoconstriction. In experimental animals (322) splanchnic blood flow decreased drastically during acceleration when the position of the animal's body was changed from a $+G_x$ acceleration position to a $+G_z$ acceleration position. Greenleaf et al. (127) measured leg blood flow in three subjects exposed to increasing levels of $+G_z$ acceleration. Flows decreased from mean resting values of 6-9 ml·min^{-1}· 100 ml^{-1} tissue to 3-4 ml·min^{-1}·100 ml^{-1} tissue.

Tissue flows, when measured during $+G_x$ acceleration, change little up to about 12 $+G_x$. Above this level, tissue compression may contribute to flow reduction. Peripheral vascular damage can occur when the intravascular pressure (or force) exceeds the tensile strength of the surrounding vascular wall. Small cutaneous blood vessels are ruptured in humans exposed to high levels of $+G_z$ acceleration, particularly around the ankles and in areas of the legs not protected by a pressure suit. The areas immediately under the pressure garment are exposed to a static counterpressure that prevents the vessels from rupturing. It is not known if human deep muscle vessels also rupture, but it does not seem likely because of the muscle pressure usually generated to sustain the high levels of $+G_z$.

In summary, with increasing $+G_z$ acceleration, cardiac output falls, stroke volume falls, heart rate increases, arterial pressure at eye level falls while the arterial pressure at the aortic arch increases slightly, cerebral blood flow falls, and the peripheral blood flow decreases. Arterial oxygen saturation decreases because of an increased shunting of blood through the lungs.

Dynamic Responses and Reflex Adjustments

The hemodynamic responses to $+G_z$ acceleration are similar to those during orthostatic stress and hemorrhage, including a reduction in arterial pressure in the head region. Activation of the arterial baroceptor reflex explains the increase in heart rate and the peripheral vasoconstriction. In 1933 Jongbloed et al. (175) sectioned the carotid sinus nerve and abolished the tachycardia response to $+G_z$ acceleration in experimental animals. Greenfield (125) found that the compensatory rise in arterial pressure during prolonged acceleration did not occur after stripping the carotid sinus region.

Other reflexogenic areas may be involved to either amplify the carotid sinus reflex or attenuate the response (32). Attenuation of the baroceptor response may occur through activation of vagal cardiopulmonary mechanoreceptors and prevent the maximum compensatory effect. Plasma levels of ADH increase during $+G_z$ acceleration (127), which is consistent with activation of cardiopulmonary receptors. Other recep-
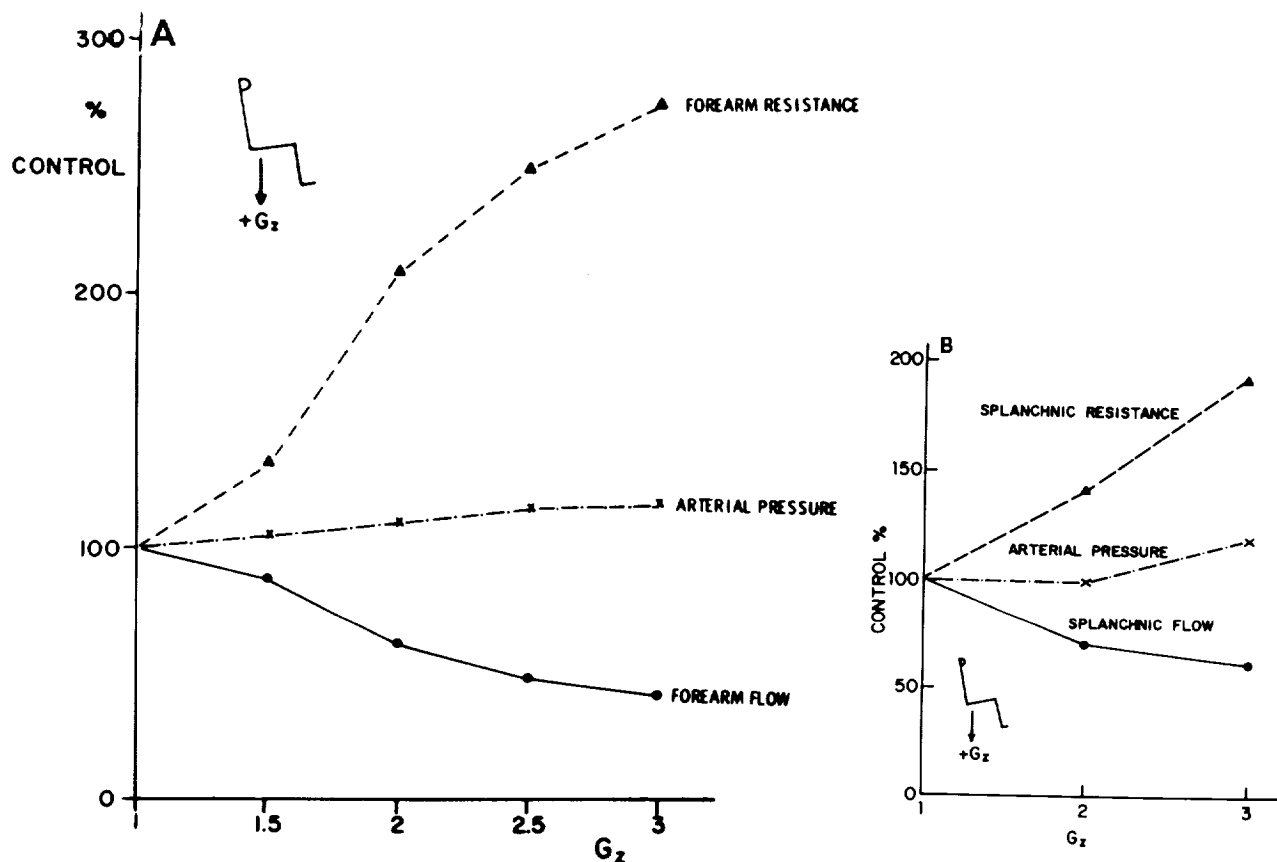
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FIG. 15. Average % change from control in forearm blood flow and resistance (*A*) and splanchnic flow and resistance (*B*) in 6 volunteers. Arm suspended at heart level throughout experiments. Arterial pressure was referenced to heart level. [Adapted from Stone et al. (318) and H. L. Stone, unpublished observations.]

tor areas, such as the splanchnic and skeletal muscle regions, could also send afferent information to the central nervous system to modify the overall responses to this type of stress. This area has not been investigated extensively and needs future work.

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Bones and Stones in Space—Integrating the Medical and Scientific Questions

Christopher E. Cann

Department of Radiology

University of California

San Francisco, CA

ABSTRACT

Bone loss and muscle atrophy are two con-
sequences of long-term spaceflight, and
neither the underlying mechanisms nor
effective countermeasures have yet been found.
Experiments designed for space station and
beyond incorporate a number of scientific
objectives focused on two interrelated con-
cepts, calcium homeostasis and bone homeo-
stasis. The experiments to be done require
a trade-off between ground based analysis
of samples and development of instruments to
do these studies inflight. The scientific
community is currently in the process of
defining which scientific objectives can be
accomplished inflight and what instrumen-
tation is required to do this.

WITH THE COMING OF THE SPACE STATION
and other possible scenarios for
long-term exposure of man to
microgravity or reduced gravity, the
major emphasis in biomedical research
and development has shifted away from
solution of the short-term
consequences of microgravity such as
space adaptation syndrome to two
major concerns, musculoskeletal
deconditioning and radiation
exposure. The short-term effects
still exist, and will be a continuing
concern for shuttle flights,
especially during station
construction. However, in planning
for long-term habitability our major
concerns are 1) to provide for the
health and safety of the crew in
flight, 2) to maintain the capability
of the crew to work efficiently under
conditions of reduced gravity, and 3)
to avoid any medical consequences on
return to earth associated with long-
term exposure to reduced gravity.
NASA and the biomedical research
community have long recognized that
these objectives can only be met
through an integrated research
program designed first to understand
the basic mechanisms underlying the
biomedical problems and then to
design countermeasures to prevent
these problems from becoming risks.
The realities of manned spaceflight
unfortunately dictate a different
approach, because in many cases we
need humans either to do experiments
with model systems or to act as
experimental subjects to get at these
basic questions. Therefore, we must
plan our program in a non-risk-free
environment, and to do this we must
anticipate the unexpected, plan for
it, and hope for the best.

PHYSIOLOGY OF BONE LOSS

Musculoskeletal deconditioning
during exposure to reduced gravity
has many facets, and we must consider
them all in our approach to this
problem. Figure 1 shows a model of
the interrelationships among the four
major components in the calcium/bone
system: blood and extracellular
fluid (ECF), intestine, kidney, and
bone. (Figure 1) Under normal
circumstances, blood calcium is
regulated very tightly at about 10
milligrams per 100 ml of serum, both
in man and in other animal species.
Deviations of as little as 0.2 mg/100
ml, or 2%, are enough to invoke

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feedback mechanisms; release of parathyroid hormone (PTH) when blood calcium drops and release
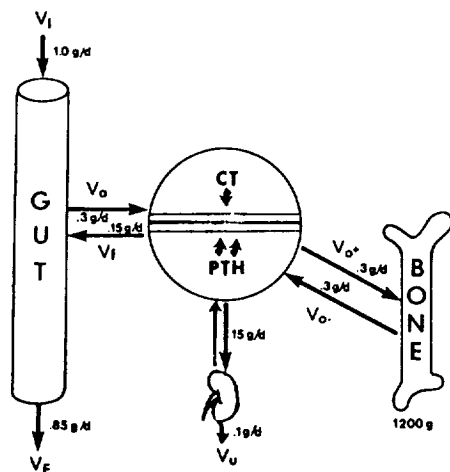

Figure 1. Representation of the relationships among various components in the calcium/bone homeostatic systems. Transport of calcium into and out of the compartments is shown in terms of grams/day.

of calcitonin when it gets too high. In actuality, it is not the total blood calcium invoking this response, but the fraction of it, about 40%, that is not bound to albumin and other proteins, that is, the ionized calcium fraction. This fraction is sensitive to many factors, including blood pH (acidity) which can be affected by CO_2 in the air, protein content of the blood, and the fraction of red cells to plasma (hematocrit). The tight regulation of blood ionized and total calcium is termed "calcium homeostasis".

The blood and ECF calcium pool is about five grams of calcium in a normal human. In our diet, we consume about one gram of calcium daily and 300 milligrams of this gets absorbed into the blood with the rest passing through the intestine. The digestive juices secrete about 150 mg of calcium back into the intestine, so net absorption is only 150 mg. Under normal circumstances, the kidney filters about 15 grams of calcium per day and reabsorbs 99%, so that only 150 mg is excreted in the urine. Bone is a dynamic organ, constantly being reabsorbed and rebuilt, at a rate of about 300 mg

per day averaged over the whole skeleton, or about 10% of total skeletal mineral per year. Some bones turn over more rapidly, such as 25% per year for the spine, and some more slowly like the femur at 1-2% per year. Bone is also a reservoir for calcium homeostasis in pathologic conditions, so that blood calcium can be maintained at the expense of the skeleton.

In the past, most studies of calcium metabolism were focused on the calcium homeostatic system described above. Recently, researchers have recognized that two interrelated systems are actually present, a calcium homeostatic system and a bone homeostatic system. This concept is extremely important, because now we can see that the skeleton is not simply a reservoir to maintain calcium homeostasis, but can actually act as an input to drive it when the skeleton responds to an external stimulus. In looking at Figure 1, we see that there are two major control points in the maintenance of skeletal integrity and calcium homeostasis. The first is the kidney. If something happens to reduce tubular reabsorption of calcium, even from 99% to 97%, urinary calcium output would triple, blood calcium would drop, and skeletal calcium would be mobilized to maintain blood calcium. The other input to blood calcium, the gut, would not begin to compensate for such a major calcium loss, so the skeleton would lose mineral over the long term. Even so, with a tripling of urine calcium we are only talking about 1% per month bone loss.

The second control point is the skeleton itself. An external stimulus with an apparent direct effect on bone, for example a major reduction in blood estrogen levels in women, can change the "set point" for maintenance of skeletal integrity, that is, the body decides it does not need the amount of bone that it has. The breakdown of the skeleton increases, dumping calcium into the blood. The calcium homeostatic system is overwhelmed and increases excretion and decreases absorption of calcium in an attempt to maintain serum calcium. After some time, the new "set point" is approached and the feedback systems return to normal. Figure 2 demonstrates this concept in

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postmenopausal women. Immobilization or microgravity apparently has a similar effect. (Figure 2.)

When normal mechanical stresses of weightbearing and muscle pulls are removed from the skeleton, breakdown of bone increases and formation
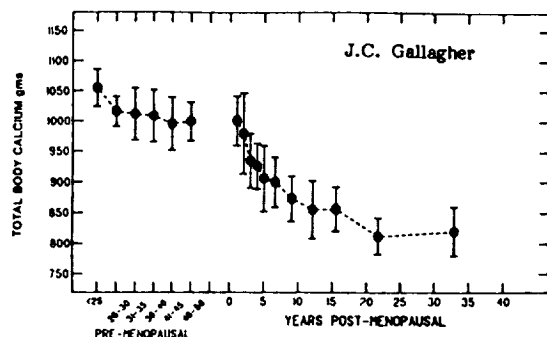

Figure 2. Total body calcium in normal, untreated women. After menopause, an exponential decline in bone mass occurs, reaching a new plateau about 8-12 years post-menopause, at a value of 80-85% of initial. This suggests that the decline in reproductive hormones (estrogen, progesterone) represent a reduction of 15-20% in the body's "need" to maintain the skeleton at its premenopausal level.

decreases. This has been well documented in immobilized and paralyzed patients (1, 2)* and in animals in spaceflight (3, 4). As with estrogen deficiency this process appears to be self-limiting (5, Figure 3).

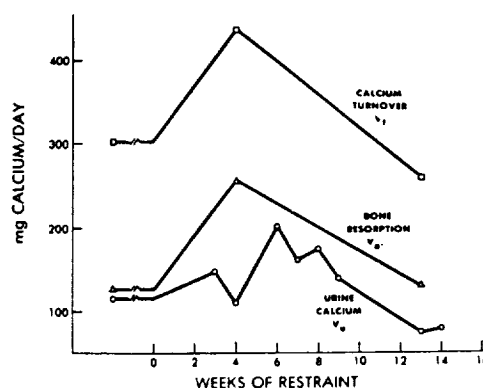* References indicated in parentheses.

Figure 3. Parameters of calcium metabolism in an immobilized monkey show an acute increase of bone to rapid bone loss, with a later resorption and urine calcium, leading return to below-normal levels after the skeleton has reached its new equilibrium.

In paralyzed adult humans, about 40-50% of total skeletal mineral is eventually lost if no treatment is given, so it appears that the "set point" for the skeleton has been reduced by this amount. We can raise this set point back to normal by restoring normal weightbearing for at least part of the time (6), or we can raise it above normal by increasing mechanical stresses on the bone (7, 8).

The design of both our basic experiments to understand how and why bone is lost in microgravity and our countermeasures to prevent this loss are underpinned by these two concepts of calcium homeostasis and bone homeostasis. The interrelationships between blood calcium, increased excretion of calcium by the kidney and risk of formation of kidney stones, the stresses exerted on bone by skeletal muscles or weightbearing-like forces, handling of calcium by the intestine, and interaction of pharmaceutical agents must be understood before we can say that bone and muscle loss is no longer a barrier to long-term habitation at reduced gravity. However, our experiments have just started, and we must now think in terms of designing new experiments with tools to solve this problem.

INSTRUMENTATION

The instrumentation we need to do biomedical and basic biological research in the musculoskeletal area is varied, and includes both inflight tools as well as ground-based systems. We can categorize the instrumentation in several ways, and I will discuss one approach based on our research questions, the model systems we use, and the types of experiments we must do both for the study of calcium homeostasis and bone homeostasis.

HABITATION - The first instrument we need for any research is a habitat for the research subjects, and that habitat will have certain requirements for both liveability and experimental procedures. For studies of calcium and bone homeostasis we have three primary animal species we use: humans, rhesus monkeys and rats. We are studying the effects of reduced gravity on these species and our long-term goal is to do experiments at zero-g, one-sixth-g, one-third-g and one-g in space, based on long-term agency objectives for man in space, lunar exploration and Mars exploration. This requires a variable gravity habitat for all three species. At the present time, perhaps the most cost-effective means of doing our research is to build a tethered system with a habitat module at one end for humans and a habitat/laboratory module at the other end for animal studies. This configuration would give us the option of zero-g (non-rotating) or up to 1 or 1.2 g with rotation about the center of the tether, would provide bioisolation for living areas, and would allow us to put sophisticated laboratory equipment in the animal module which could double for analysis of human samples brought over from the human module. In addition, because we would have isolated the animal module completely we can more easily use two radioisotopes we require for much of our work, carbon-14 and tritium, without worrying about C-14-carbon dioxide in the air or tritiated water in the condensate recovery system for the human module. We can also control the atmosphere in the animal/lab environment to do such experiments as the effect of atmospheric CO_2 on blood chemistry in microgravity. The requirement to

make a man-rated habitat at 1 g would define the length of the tether, and we would have no problem with coriolis forces in our monkey or rat studies.

Included in the design of the habitat must be a means for continuous and/or periodic waste collection for metabolic studies in all species. In rats, while urine collection and separation from feces is desirable, it is difficult even in our ground-based studies because urine volume is so low. This is not a major concern, however, because calcium output in rat urine is also quite low, and combined urine/fecal collections have been used quite successfully in flight experiments (9). For rhesus monkeys, long-term (90-120 days) habitation is a more difficult problem. First, a cage must be designed which allows complete monitoring of food and water intake, collection of waste, separation of urine from feces at least some of the time, and access to the animal for health purposes while maintaining bioisolation. A waste management system that works must also be designed for the human habitat.) An additional requirement for experimental purposes with the monkey is the capability to remove the monkey from the habitat into an experimental module such as the RHEC, developed by the French as part of the ESOP facility for large primates to be flown on Spacelab. This will allow hands-on provocative testing to be done with the animal restrained for short periods of time during a long-duration mission.

GENERAL LABORATORY EQUIPMENT - Many of the studies proposed for space station and beyond in the bone/calcium discipline require general laboratory equipment already developed or under development for Skylab or Shuttle/Spacelab. This includes such equipment as a blood drawing kit, refrigerated centrifuge, 4 C refrigerators, -20 C and -70 C freezers, work station with microscope and small animal surgery area, and the like. However, there are three approaches to the development and use of more experiments-specific but still generally useful equipment. First, we can define those measurements which must be made in flight either non-invasively or because samples

obtained must be fresh and cannot be fixed or frozen. This includes such things as blood gases and ionized calcium measurements and measurements made non-invasively for which the time course is the highest scientific priority such as regional bone and muscle density and volume or tissue perfusion. Equipment to make these measurements must be flight qualified. Other samples can be obtained, minimally processed, frozen or fixed, and returned to ground-based laboratories for analysis, or pre and postflight non-invasive measurements can be made on experimental subjects. This first option requires, in addition to some equipment development, a significant amount of stowage and sample return capability. It has the advantage that when a sample is returned to an investigator's laboratory the same high quality, high precision measurements made on routine specimens can be made on these samples, and also has the advantage that other analyses not planned for originally but of significant scientific interest can be done. The disadvantage is that measurements cannot be made during the course of the experiment, the data interpreted, and the experiment modified if necessary to optimize the scientific output. For human studies, it also has the disadvantage that clinically-relevant changes occurring in individuals may not be apparent until postflight measurements are made.

The second option is the development of most or all of the instrumentation needed to make measurements inflight. The main advantage of this option is that it substantially reduces stowage and sample return requirements. Additionally it allows data to be transferred to the investigators during the course of an experiment, allowing them to modify the experimental protocol in near real time. The disadvantages of this approach module 1) loss of precision of measurements compared to an investigator's laboratory, 2) the need to train astronauts in many more laboratory techniques than is currently done, 3) increased crew time requirements, and 4) long lead time to develop sophisticated automated analysis and testing instruments, many of which do not

currently exist even in the laboratory.

The third option is a mix of the first two, with a balance between their advantages and disadvantages. this would include development and flight qualification of instrumentation that the scientific community feels can be used to make measurements with sufficient accuracy and precision to satisfy their scientific requirements. For example, the simple serum chemistry analyses developed for the Health Maintenance Facility lab will not begin to suffice for research purposes, but flight qualification of a routine blood gas anlyzer will do. Of particular interest will be capabilities to measure minerals and other materials in exreta for metabolic studies, because this will comprise a large fraction of the stowage requirements for the bone/calcium discipline.

EXPERIMENT-SPECIFIC INSTRUMENTATION-Some scientific objectives in the bone/calcium discipline require specific instrumentation. High precision, high accuracy instruments have been developed for NASA for pre and postflight measurements of bone and muscle density and volume. Figure 4 shows a schematic of part of the Computed Tomodensitometer (CTD), a computed tomography scanner designed and built for delivery to Johnson Space Center by the University of California, San Francisco. This device will measure bone density in any region of the body, in three dimensions, with an accuracy and precision of better than 0.5%. It can also do routine CT cross-sectional imaging to detect kidney stones, for example, and can be used for tissue perfusion measurements (using inhaled stable Xenon gas), cardiac dimensions using ECG-gated CT, or other studies requiring three-dimensional imaging/density capabilities. The prototype device is a ground-based model, but the system design is inherently low power, low mass and low volume, so it can be optimized for a flight instrument. Some of the highest priority science objectives in the bone/calcium discipline, especially for human subject, require determination of the time course of regional changes in bone density,

both the natural course and the
changes that may occur in response to
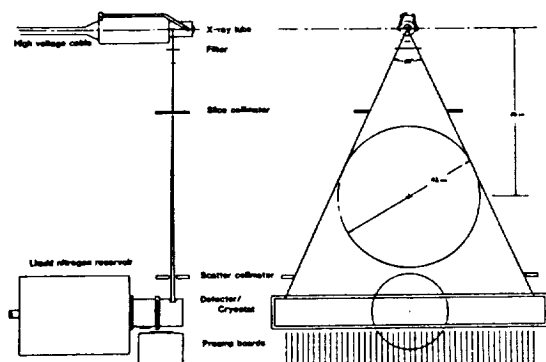specific exercise regimens used as

Figure 4. Diagram of the
source/detector system of the
UCSF/NASA Computed Tomodensitometer.
The source is a low-power, heavily
stabilized and filtered x-ray tube
producing a dual-energy photon
spectrum simulating a radioisotope
such as gadolinium-153, but with 50-
100 times the output.   the detector
is high-purity germanium, cooled
either with liquid nitrogen or a
small refrigerator with a capacity of
a few watts. the custom data
acquisition electronics count photons
at 1 MHz per channel, 2 channels peer
detector, 360 detectors, and dump
data to a VME-compatible system for
processing.

possible countermeasures. this is
especially important in light of
recent evidence that even 2-3 hours
per day of exercise may not be
sufficient to protect against muscle
atrophy in flight (10).
    Several other instruments will
have to be developed and flight-
qualified to investigate specific
problems in the musculoskeletal area.
Non-invasive measures of bone quality
or mechanical strength will be
necessary in serial studies in humans
and monkeys. Some use of
radioisotopes will be required in
experiments in rats and monkeys,
necessitating proper handling
procedures. Long half-life isotopes
may be used, but some studies may
require the use of on-board counting
facilities. Alternatively, stable
isotopes may be used as tracers, with
return of samples for analysis
processing bone specimens from rats
or monkeys will be necessary,

including such items as vacuum ovens,
microtomes antoradiographic
materials, and microscopes with video
interface. It may be of interest to
eventually develop a nuclear magnetic
resonance (NMR) spectrometer to do
in vitro or in vivo small animal
metabolism studies of phosphorus,
carbon-13 and hydrogen-containing
compounds. In general, most of the
instrumentation we need for specific
experiments exists in the laboratory.
It just remains to 1) decide whether
we need it in flight, based on our
choice of the options presented
earlier, and 2) develop flight-
qualified versions that can perform
up to the standards we set for
obtaining high-quality scientific
results.

SUMMARY
    Musculoskeletal research for
space station and beyond is high
priority because of the adverse long-
term consequences to crew health and
performance due to muscle and bone
atrophy. Research is driven by two
concepts, calcium homeostasis, or
maintenance of normal blood calcium
levels, and bone homeostasis, or the
response of the skeleton to its
environment. Scientific objectives
require the use of multiple species
to do experiments, including humans,
rhesus monkeys and rats, and the use
of a variable gravity habitat for all
three species. Much of the general
laboratory instrumentation needed for
experiments has been developed
previously, but specific items remain
to be optimized and flight qualified.
Most equipment for specific
experimental objectives exists in
ground-based laboratories, but for
high-priority studies this equipment
must be further developed flight-
qualified.

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Cell Sensitivity to Gravity

Abstract. *Cultures of human lymphocytes exposed in microgravity to the mitogen concanavalin A showed less than 3 percent of the activation of ground controls. This result supports the hypothesis, based on simulations at low g and experiments at high g, that microgravity depresses whereas high gravity enhances cell proliferation rates. The effects of gravity are particularly strong in cells undergoing differentiation.*

An answer to the question of whether cells are sensitive to gravity was one of the objectives of experiment 1ES031, on the effect of weightlessness on lymphocyte proliferation, performed on board Spacelab 1. Another objective was to establish, by exposing cultures of human lymphocytes to a mitogen during spaceflight, whether functional changes occurred in the cells responsible for the immune response. Several investigators (*1*) reported that lymphocytes from the majority of crew members on U.S. and Soviet space missions had a decreased response to mitogen after flight. Stress may be one of the reasons for the reduction of lymphocyte response (*2*). A manifold increase of induced interferon pro-

duction was recently observed in cultures of human lymphocytes flown on the Soviet space station Salyut 6 (*3*). One of the few experiments dedicated so far (*4*) to the study of the effects of microgravity on cells was performed on Skylab with a strain of human embryonic lung cells, WI-38 (*5*). Although there were no significant changes in cell proliferation and motility, glucose consumption was significantly lower in the cells flown in space.

On Spacelab 1 we exposed cultures of human lymphocytes to concanavalin A (Con A), a mitogen capable of transforming resting T lymphocytes into activated (dividing) cells. This is a suitable model for the study of certain aspects of the immune system and of cell differentiation in vitro. In addition, in connection with the experiment on Spacelab, we studied the adaptation of animal cells to an altered gravitational environment and found that proliferation of five types of cells is remarkably enhanced at 10 *g* (*6*), whereas glucose consumption is the same at both high *g* and 1 *g*. However, cell motility is hindered at 10 *g*. In particular, lymphocyte activation is strongly gravity-dependent; the proliferation rate is almost doubled at 10 *g*. We suggest that, under gravitational stress, the cell is capable of switching to other metabolic pathways (*6*). Conversely, when lymphocytes are cultivated at simulated microgravity in a rapidly rotating clinostat, in which gravity is changed from a vector to a scalar in the presence of Con A, activation is depressed by 50 percent (*7*). In general, hypergravity promotes cell proliferation, whereas microgravity has a depressing effect. Our experiment on Spacelab 1 was designed to test this hypothesis. All preflight operations and the synchronous ground control experiment were performed at Kennedy Space
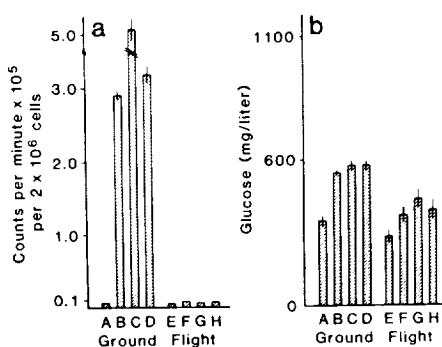

Fig. 1. Lymphocyte activation induced by Con A in microgravity. Cultures of human lymphocytes were exposed to mitogenic concentrations of Con A in ground samples B, C, and D and flight samples F, G, and H, respectively. Samples A (ground) and E (flight) were unstimulated controls. (a) Activation measured after 69 hours incubation at 37°C as [^{3}H]thymidine incorporation into trichloroacetic acid–precipitable material. (b) Glucose remaining in the medium measured by the glucose dehydrogenase method (*6*). The initial concentration of glucose in the medium was 1100 mg/liter. The standard deviation of triplicate samples is given, except for samples A, E, F, G, and H in (a), for which it was too low to be shown here.

Center. The analysis of the flown and control samples was performed in Zürich.

The apparatus (4) consisted of a carry-on incubator operating at 37°C, containing four cell culture flasks, syringes with mitogen, ^{3}H-labeled thymidine, and hydroxyethyl starch (HES) as a cryopreservative. Twelve hours before launch, lymphocytes were purified from human blood and resuspended in culture medium (6) at a final concentration of 2×10^6 cells per milliliter. Portions (8 ml) of the culture were sealed in eight flasks: A, B, C, and D were the ground control samples and E, F, G, and H the flight samples. The flight incubator was carried on board 6 hours before launch; 6 hours after liftoff the incubator was installed and switched on. The experiment was activated by injection of Con A (25 µg/ml) into three flight and three ground cultures. The fourth ground (A) and flight (E) cultures were unstimulated controls. After 69 hours of incubation, radiolabeled thymidine was injected into cultures to give 4 µCi/ml. Two hours later HES was added to a final concentration of 14 percent. Air was let into the flasks and, after vigorous shaking, the cell cultures were stored in liquid-nitrogen freezers both on board and on the ground until the end of the mission. Finally, 13 days after completion of the experiment all cultures were simultaneously thawed and prepared for analysis.

The main result is given in Fig. 1. The activation of the flight samples, measured as incorporation of tritiated thymidine into DNA, is less than 3 percent that of the ground controls (Fig. 1a). However, the cells survived the space flight, since the glucose consumption is only slightly lower in the flown than in the ground samples (Fig. 1b) and a significant number of radiolabeled nuclei are found by autoradiography of the lymphocytes exposed in flight to Con A (Fig. 2). The fact that glucose uptake seems not to be significantly altered by microgravity suggests that other membrane properties, such as binding of Con A and thymidine uptake, are also not dramatically changed. (The observation of lymphocyte aggregation in microgravity implies Con A binding to the surface membrane.) Many more nuclei are labeled in the activated cells at 1 g. Preliminary data from scanning and thin-section electron microscopy do not indicate significant structural differences between control and flown cells. Although the results are unequivocal, we note that they are from a single experiment and therefore need to be checked on future missions.

In the following discussion we assume that the constituents of cosmic radiation which can penetrate the culture flasks—that is, high-charge and high-energy particles such as iron nuclei—do not play a relevant role in this experiment. In fact, the probability that a significant number of resuspended cells are hit by the radiation in cultures containing 16×10^6 cells per flask is extremely low.

As discussed above, a decrease of lymphocyte reactivity was expected; however, the extent of the depression is surprising. Lymphocyte activation is triggered by at least two signals. In our experiment, the mitogenic signal is delivered specifically to T lymphocytes by Con A through its binding to glycosidic residues on the cell membrane followed by patching and capping. The second signal may be delivered by factors produced by macrophages (which are always present in lymphocyte cultures) and/or by subpopulations of T lymphocytes (interleukins). A third signal may be required and delivered through direct cell-cell contacts; although the finding of high activation in cultures diluted to as few as 5×10^4 cells per milliliter does not support the necessity of cell contacts. While the first two signals should reach the cell in microgravity, the third signal may be hindered since cell-cell contacts may be less probable in lymphocytes suspended at 0 g. However, the following considerations indicate that cell contacts must also occur in microgravity: (i) aggregates of cells, although less frequent, were formed in microgravity (Fig. 2); (ii) an experiment flown on the eighth space shuttle mission showed that contacts between cells and

Fig. 2. Light microscopic autoradiography of (a) ground and (b, c) flown lymphocytes exposed to Con A. Cells were fixed on glass slides with 5 percent trichloroacetic acid, rinsed with water for 24 hours, and coated with L-4 nuclear research emulsion (Ilford). After exposure for 7 days the slides were developed, fixed, and treated with Giemsa stain. Scale bar, 10 µm. (a) Most of the Con A-treated cells in the ground samples formed aggregates with labeled nuclei, as shown here. (b) Similar aggregates were formed in microgravity; however, their occurrence was markedly lower than at 1 g. (c) Single cells with labeled nuclei in the flown samples indicate that aggregation may not be necessary for activation.

microcarrier beads are at least as effective in space as on the ground (unpublished results); (iii) passive cell movements in the medium, which may contribute to establish cell contacts, are not hindered by gravitational forces; (iv) calculations based on the volume of the flask and the cell concentration show that the average statistical distance between cells was less than 0.05 mm in our cultures; and (v) considering the various signals involved in activation, it is important to note that the comparative results in Fig. 1a are consistent with activation being an all-or-none phenomenon.

Although our observations are in agreement with the results found with lymphocytes taken from crew members after spaceflight, we cannot extrapolate the data derived from experiments in vitro to changes occurring in vivo. Experiments planned for the D-1 and Spacelab 4 missions in 1985 and 1986 should clarify the question of lymphocyte efficiency in space.

Considering what is presently known about the behavior of cells at different *g* values, we can see a relatively consistent picture into which our results from Spacelab 1 fit very well. At high *g*, cells divide faster at the expense of reduced motility, since energy consumption remains the same. In microgravity, lymphocytes show a dramatic reduction in proliferation rate, reduced glucose consumption, but a strong increase of interferon secretion. WI-38 embryonic lung cells, which differ from lymphocytes in that they do not undergo differentiation steps, grow and move normally at 0 *g*, but they also consume less glucose. In conclusion, most of the cells investigated appear to be sensitive to gravity; the effect seems to be stronger with cells such as lymphocytes, which are transformed by mitogens from a dormant to an activated state.

The results we have obtained so far have contributed to an increase in the knowledge of the influence of gravity on basic cellular mechanisms, to clarifying certain biomedical aspects of the effect of spaceflight on the immune system, and to developing useful biotechnological processes. Although the mechanisms involved in gravitational effects on cells are still unknown and a gravity sensor has not yet been identified, we can conclude on the basis of results to date that cells are sensitive to gravity.

A. COGOLI
A. TSCHOPP, P. FUCHS-BISLIN
Laboratorium für Biochemie,
Eidgenossische Technische Hochschule,
CH-8092 Zurich, Switzerland

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8. Supported by the Swiss National Science Foundation (grants No. 3.034-81 and 3.382-0.82) and by the Board of the Federal Swiss Institutes of Technology. We thank E. A. Fellmann for calculating the average distance between cells in microgravity, B. Huber for his contribution to manufacturing the incubators, and M. Valluchi-Morf for her excellent technical assistance in the first phase of this project.

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A. Cogoli, T.H. Iversen, A. Johnsson, D. Mesland & H. Oser

Introduction

Gravity exerts a fundamental influence on Earth organisms. This will sound like a truism to many scientists, but the fact is that the importance of the gravitational force for life-sciences research was never really faced until the space age dawned. Some very basic physical processes work quite differently under normal Earth gravity (1 g) and under so-called 'microgravity' conditions. But it is not just that fundamental physical processes are different in microgravity: since these physical processes are involved in many biological processes, biological systems may also be altered or affected in new ways.

While it is conceivable that a complex organism like a human body experiences a number of effects in a microgravity environment, it is much more difficult to accept that a single cell may perceive gravity. Calculations based on the physical properties of the cell membrane, organelles and cytoskeleton seem to predict that no gravity effect may be expected at the cellular level. However, most of these considerations look at the cell as a static and unchangeable system, and do not account for the countless single events occurring in sequence or in parallel in a living cell during differentiation, proliferation and gene expression. All this machinery has developed under 1 g conditions, i.e. it is designed to make optimum use of gravity during differentiation, proliferation and gene expression. Evolution at 1 g has probably ruled out the unfavourable alternative pathways leading to failures in the cellular functions. The system did not have the chance to go through evolution at zero g and to exclude these unfavourable pathways.

The discussion on microgravity effects in the context of cell biology presented below is by no means complete: only a few areas will be touched upon, but they have been chosen to demonstrate how microgravity will open up important new areas in the study of the life sciences.

Biophysical Aspects

Decreased pressure/strain in cells and organisms

An obvious effect of reduced gravitational force is that the physical pressures and loads in organisms and cells change. An example of how the physical strain on structures changes is given in Figure 5.1, from cellular biology. Of course, examples could just as well have been chosen at organism level: the pressure in the body as a whole changes under microgravity.

The reduction in pressure and strain will be of the utmost importance in many areas of both plant and animal physiology. Besides those involving human and animal physiology, which have been discussed in earlier chapters, we can note:

− studies of the consequences of changes in membrane stress
− studies of the shape or organism, gravimorphism, etc.
− studies of the cytoskeleton.
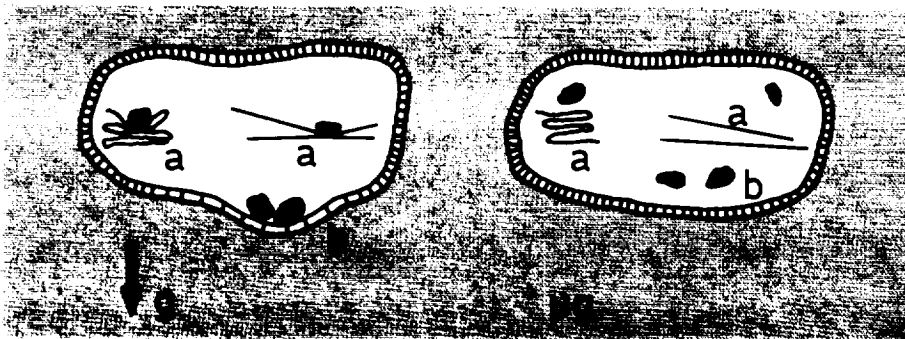
Figure 5.1. Physical strains are different under 1 g conditions and in space, i.e. under microgravity conditions. To the left is illustrated, in a schematic and simplified way, how internal masses (a) can cause load and strain on internal cell structures; strain in cellular membranes can likewise increase due to cellular masses or cell content by itself (b).
Such strains are more or less absent when the system is moved to microgravity, as shown in the sketch on the right.

Sedimentation of particles, buoyancy of bubbles, etc.

Another obvious, but fundamental effect of reduced gravitational force is that sedimentation of particles in fluids is diminished or even totally absent (Fig. 5.2). Correspondingly, gas-filled volumes, vesicles, etc. will not move as effectively, because of reduced buoyancy, or will simply remain in place under microgravity conditions.

The absence of sedimentation and buoyancy under microgravity will enable life scientists to carry out fundamental studies of:

— the perception of gravity and forces
— the overall balance systems of plants, animals, man, etc.

Figure 5.2. Schematic of particle sedimentation in a plant cell. To the left, under 1 g conditions, the denser black particles have sedimented to the lowermost part of the cell.
To the right, under microgravity conditions, no settling occurs and the particles are almost evenly distributed in the cell volume.
n = nucleus;
v = vacuole
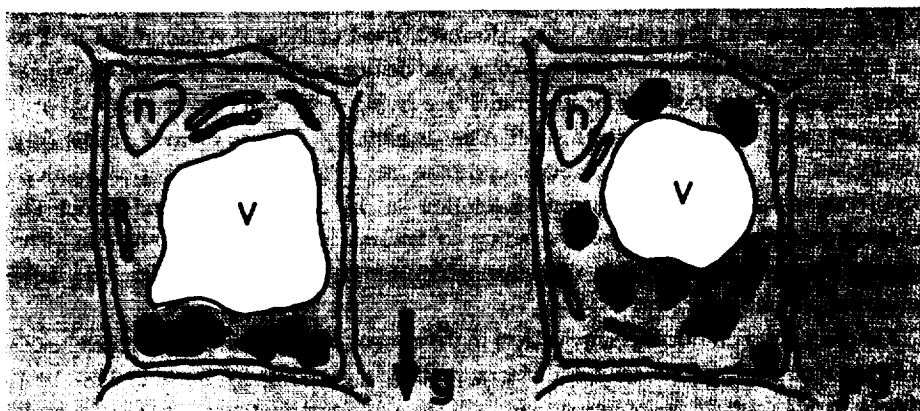
Stirring/convection

When density gradients are present in a liquid or gas under normal 1 g conditions, stirring and mixing take place. Because of this movement, the gradients ultimately disappear. A thermal gradient induces convection and mixing in the same way.

In microgravity, such mixing effects simply do not occur (Fig. 5.3). This absence of mixing is of interest not only to physicists and material scientists, but also to the life scientist, since studies under space conditions are likely to yield interesting results in many relevant areas in terms of:

— mixing processes in organisms
— diffusion-controlled processes
— limitations (in the absence of stirring) of the transport of material into and out of the cell through the cell membrane, e.g. by exchange of electrolytes, etc.
— other convection phenomena that may occur in microgravity.

Figure 5.3. Natural mixing and convection disappears under microgravity conditions.
To the left is a schematic of how molecules are transported over a membrane along a concentration gradient. The transport occurs with a certain flow velocity v, under 1 g conditions. Mixing due to density gradients, etc., influences the systems and introduces a 'stirring effect' which facilitates the transport.
To the right, mixing is absent in microgravity. Fewer 'stirring effects' are introduced and the transport of molecules across the membrane will be affected and slowed down compared to 1 g.
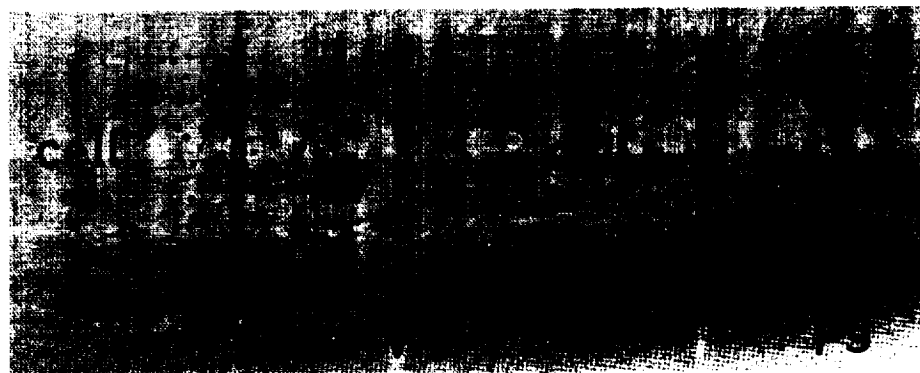
Changes of surfaces

Under normal 1 g conditions, gravity often inhibits increases in the size of bubbles and drops. Surface forces and phenomena depending on flow are easier to study under microgravity conditions. For example, the height of a liquid column in a capillary will be much greater in microgravity, because of the relative increase in surface tension in proportion to gravity (Fig. 5.4).

Several processes that must also interest the life scientist will therefore be affected in space:

- transport processes in organisms
- uptake processes by, for example, plants and roots
- growth processes as a consequence of the effects on transport processes
- transport in artificial soil materials, etc.
- all phenomena connected with the creation and existence of surfaces (including vesicles and membranes), etc.

Bioprocessing in space

The processes mentioned above may change mechanisms governing fundamental cellular functions. These alterations may be exploited for bioprocessing in microgravity. One of the tasks on future space missions will be the selection of biological systems suitable for bio-technological applications.

In addition, it is of great importance to the life scientist that the separation and isolation of biological specimens (molecules, particles, cells) is also effected. The key concept here is one of 'bioprocessing in space', and this will be dealt with in more detail in Chapter 9.

The absence of convection and sedimentation is crucial to many bioprocessing techniques that need to be investigated in space. These range from the very fundamental production of protein crystals for basic life-sciences research, to the delicate fabrication and separation of minute amounts of highly important medical substances. One of the most widely used analytical techniques is electrophoresis. It will be important to establish whether electrophoresis, in combination with the absence of convection in liquids under space conditions, might be used for the separation of biological materials in quantities and with purity levels unattainable on Earth.

Figure 5.4. Rise of a liquid in a capillary under Earth and space conditions.

The importance of surface forces relative to hydrostatic forces will increase in space, where the latter are drastically reduced. An example is given here.

A liquid rising due to capillary forces to a height L in a capillary (diameter 2R) at 1 g is shown in (a). It will rise to a much higher level when the g force is reduced.

To the right (b), the force is reduced to 10^{-4} - 10^{-3} g (a value expected in Spacelab), and the liquid column will now be 1000-10000 times higher if the diameter and the liquid remains the same.

What Do We Know Today?

Unicellular and mammalian cells

The behaviour of single cells in space was first studied on the early biosatellites launched in the mid-sixties. Unfortunately, the lack of proper controls, and technical failures, often impaired the scientific credibility of early investigations.

Only a selection of the experiments that contributed significantly to the progress of cell-biology experiments in space are discussed here. The most interesting changes that have been observed in microgravity are summarised in Table 5.1. Historically, at least as far as US missions are concerned, two periods can be distinguished: the pre-Shuttle and the Spacelab/Shuttle eras. Most of the projects carried out in the first period have been reviewed earlier. A clear effect of space flight (i.e. microgravity and cosmic radiation) on bacterial growth was discovered in an experiment performed on Biosatellite-II in 1967. The objective of the investigation was to study the effect of radiation on the propagation of bacterial growth. Both organisms tested, namely *Salmonella typhimurium* and *Escherichia coli*, exhibited a significantly higher cell densities in space than in the ground controls.

A few years later, the effect of space flight was studied on WI-38 human embryonic lung cells in a tissue culture package — called 'Woodlawn Wanderer 9' — installed on board Skylab. This was probably the most sophisticated equipment for cell cultures ever used in space. The authors reported that no effect of microgravity was detected on the cells investigated. However, the significance of the marked reduction in glucose consumption has been ignored. In fact, this result clearly indicates that the metabolism of the cells was changed in microgravity. Changes in metabolism and in the cell cycle were discovered in a unicellular organism (*Paramecium tetraurelia*) during a flight on a Soviet mission. Moreover, the resistance of bacteria to antibiotics was increased

Table 5.1. Alteration of cellular functions in microgravity

Cell Type	Function Altered	Investigator
Human embryonic lung cells	*Energy consumption:* 20% reduction in glucose consumption	Montgomery
Human lymphocytes	*Biosynthesis:* 500% increase in interferon production	Bàtkai, Tàlas
	Differentiation:[1,2] 90% depression of activation by Con A	Cogoli
Escherichia coli	*Conjugation:*[1] 400% increase in DNA transfer	Ciferri
	Membrane permeability:[1,2] Increased resistance to antibiotics	Tixador
Paramecium aurelia[2] Chlamydomonas R. Bacillus subtilis Anis cells	*Cell proliferation:*[1] Manifold increase in biomass yield	Planel Mergenhagen Mennigmann Theimer
Physarum polycephalum	*Intracellular convection:*[1] Increase in frequency and velocity of cytoplasmic streaming	Briegleb

[1] Experiments with an in-flight 1-g control
[2] Results obtained from independent experiments on at least two different space missions

in space. In addition, experiments performed on two different space flights reported that the biosynthesis of interferon in-vitro is approximately five times greater in space.

An important step towards large-scale cultures of substratum-dependent mammalian cells was performed on the Space Shuttle 'Challenger' (flight STS-8) in 1983. The fact that cells adhere normally to Cytodex microcarriers, even though resuspended in microgravity, shows that no restriction is imposed on the culture of adhering cells in space.

The advent of Spacelab opened up access to biological experiments in microgravity to a broader community than in the past. In particular Biorack, a facility provided by ESA, hosted several successful experiments with single cells on the German Spacelab-D1 mission in 1985. These investigations have shown that single cells in cultures are sensitive to gravity, i.e. that important cellular functions are affected by low-g conditions. Due to their importance, these results are discussed in more detail below.

The effect of gravity on lymphocytes in-vitro has been studied extensively under microgravity in space, in simulated low-gravity in the clinostat, and in hypergravity. A synopsis of the results is given in Figure 5.5. Lymphocytes are easily purified from peripheral blood and can be activated chemically or by exposure to mitogens in culture. Mitogens are substances from different origins (many from plants) having the property of binding to components of the cell membrane (mostly to sugar moieties of membrane glycoproteins). When mitogens like Concanavalin A (Con A) interact with lymphocytes, T-cells undergo a series of changes (activation), leading ultimately to cell division (mitosis). T-lymphocytes secrete lymphokines (IL-2,IL-3, IL-4 as well as interferon). The mechanisms of the activation in-vitro are analogous to those occurring in-vivo when the immune system is challenged by antigens. The main difference is that antigen activation is based on clonal selection of a restricted population of cells, whereas mitogenic activation is polyclonal, i.e. involves all T- and/or B-lymphocytes. Altogether, lymphocytes are a good model for fulfilling the goals of investigations in three main areas of gravitational biology:

- basic science, i.e how gravity affects differentiation processes
- biomedical diagnosis, i.e. how the immune system of astronauts adapts to spaceflight conditions
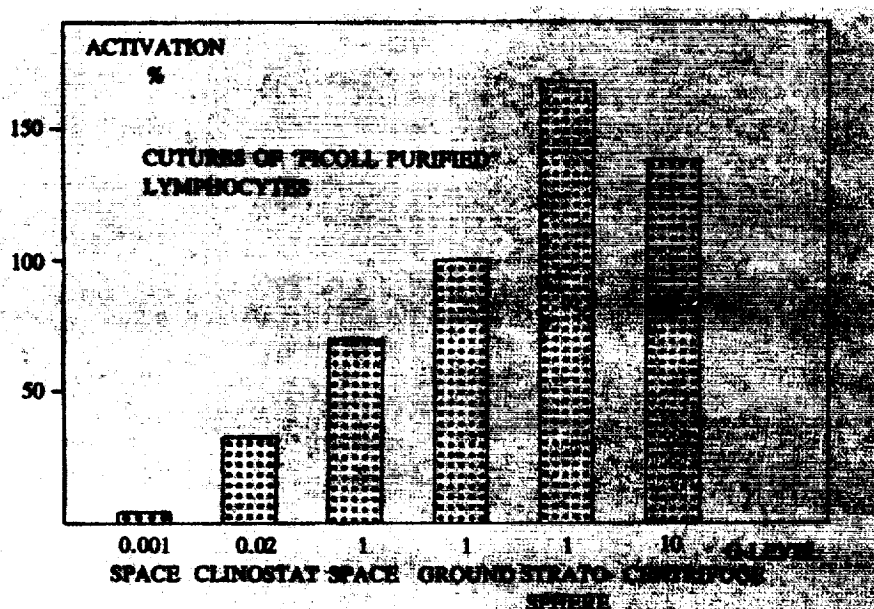

Figure 5.5. Summary of gravitation and cosmic radiation effects on T-lymphocyte activation by Con A. The results are expressed as percentages of the corresponding 1 g control. The increase at 10 g is due to the simultaneous activation of T- and B-lymphocytes.

— biotechnology, i.e. how the production of important substances (like interferon and interleukines produced by T-lymphocytes) may be qualitatively and quantitatively improved in space.

The results of three independent experiments showed that lymphocyte activation is depressed by more that 90% in space. Figures 5.6 and 5.7 compare the ultrastructural differences observed by transmission electron microscopy between cells cultured in space at zero g, and at 1 g, respectively.

Combining the results on mitogenic activation with those on interferon production, one may speculate that in microgravity lymphocyte proliferation is depressed in favour of the biosynthesis of an important product like interferon. This does not necessarily mean that plants for interferon production should be set up in space; rather lymphocyte behaviour in space can be considered as an example of a mammalian cell undergoing changes that may be of biotechnological relevance if detected in other cell systems.
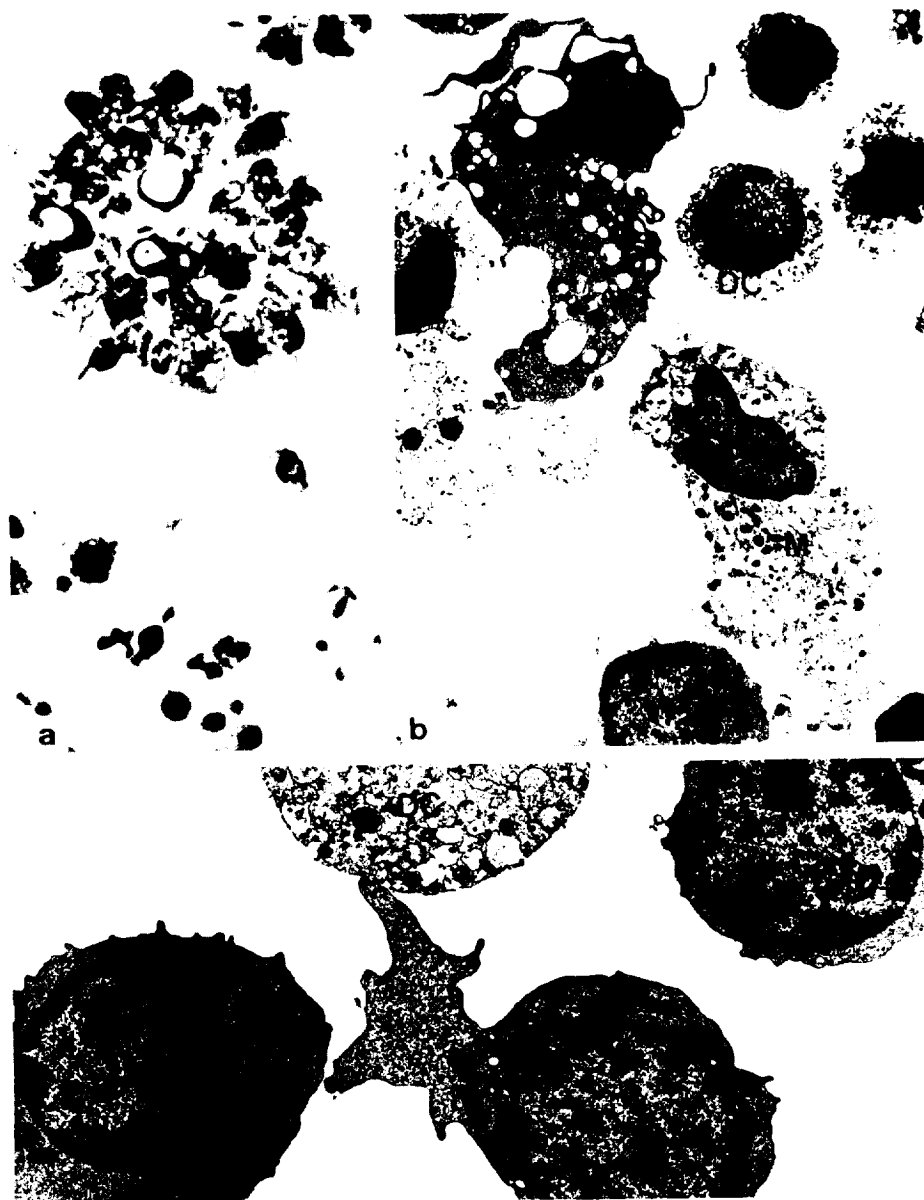

Figure 5.6. Light and electron micrographs of in-vitro cultivated cells under microgravity conditions. (Courtesy of O. Müller)

(a) Cluster of vaculated macrophages (x1000).

(b) Two macrophages (M), dead cells (DC), and cellular debris and part of a normal lymphocyte (x5100).

(c) Three morphologically normal lymphocytes, one of which shows pseudopodia (*), and part of a degenerated cell (DC) at day 4 at zero g (x10000).

Plant cell biology studies

As mentioned previously in Chapter 4, the development of plants from single somatic cell cultures is likely to be a fruitful area of investigation under microgravity conditions.

The use of plant cell cultures in space biology dates back to the joint US-USSR studies on the Soviet Biokosmos missions, during which preliminary experiments were performed using carrot cells. On the unmanned satellite missions Kosmos 782 and 1129, it was investigated whether free carrot cells, because of their totipotency and capacity for organised development, could undergo embryogenesis under microgravity conditions. It was found that morphogenetically competent carrot cells could give rise to embryos and that the latter could further develop small plantlets in about 20 d in darkness. After flight, normal plants were grown to maturity from these samples.
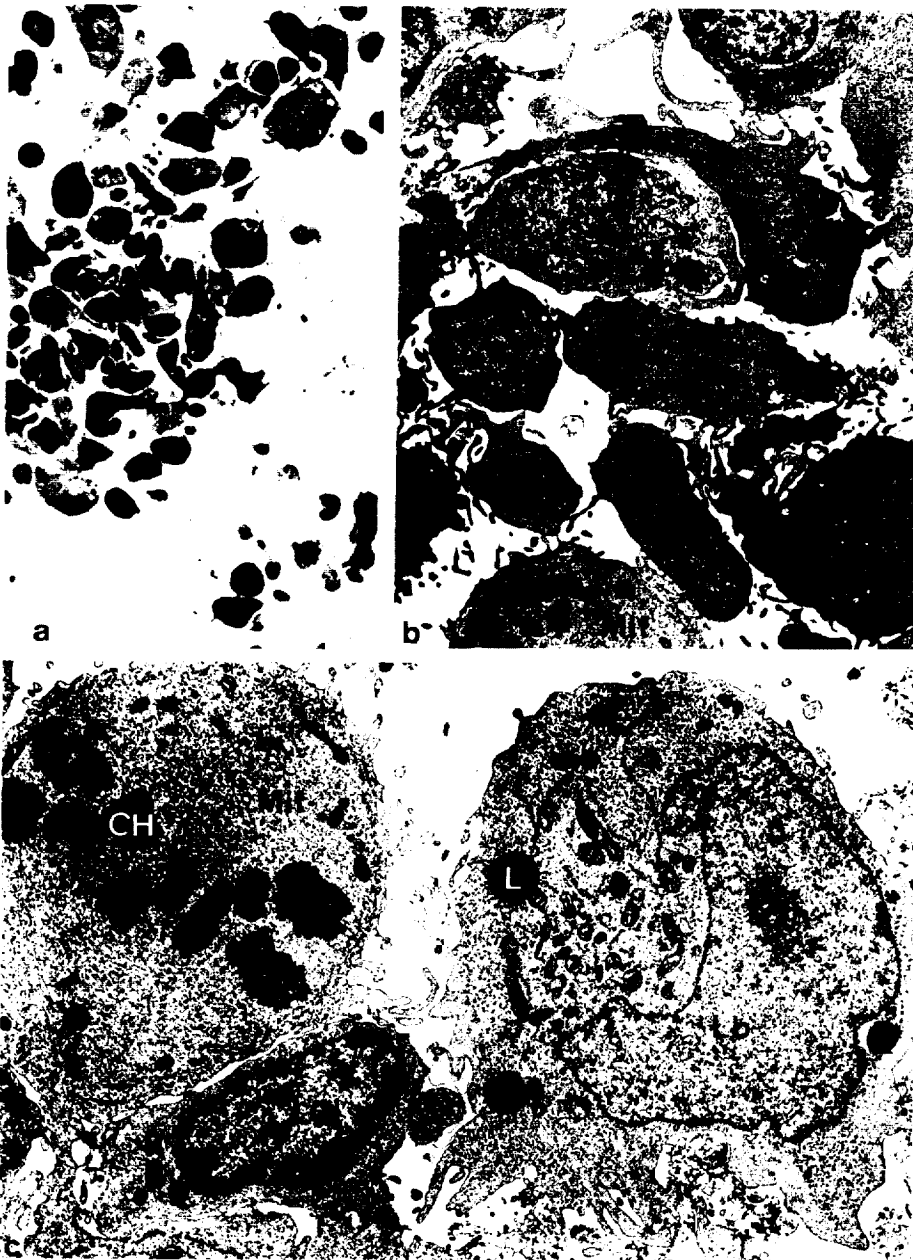

Figure 5.7. Morphology of in-vitro cultivated cells at 1 g in the reference centrifuge on board Spacelab. (Courtesy of O. Müller)
(a) Light micrograph of a lymphocyte-lymphoblast (LC) aggregation at day 3 (x1000).
(b) Higher magnification (x4500) of aggregated cells, one being in mitosis (Mit.).
(c) A lymphocyte (LC), a lymphoblast (LB) with lipid droplets (L), and a lymphoblast in metaphase showing chromosomes (CH) and spindle fibres (arrows) at flight day 4 (x8200).

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In the domain of cell biology, plant cells can be subdivided into two types:
- unicellular plants
- protoplasts.

Unicellular plants

An experiment with the unicellular algae *Chlamydomonas reinhardii* was performed in the Biorack on the Spacelab-D1 mission. The aim was to study the biological clock and other cellular functions such as swimming velocity, proliferation, viability and ultrastructural alterations. It appears that the circadian rhythm of the algae was not influenced by space flight. Similar experiments are planned for the Space Station. It is recommended that an algae colony be developed directly under microgravity, starting from single cells to form a colony that can then be cloned. From these clones, one particular colony should be selected and developed under constant temperature and light conditions until flagella have been formed. These cells should then be used for the experiments.

The most important problems that can be addressed using unicellular plant cells are:
- the correlation of motility and energy consumption
- survival rate
- ultrastructural studies.

Protoplasts

Protoplasts are plant cells whose cell walls have been removed enzymatically. Only a few experiments with plant-cell cultures have been carried out in space. However, investigations of this kind have been suggested, and a morphogenetic study on protoplasts has been accepted for Biorack on IML-1 and Biokosmos-9.

On the Space Station, it would be possible to pursue and extend studies using protoplasts and plant-cell cultures. The following experimental tissue culture systems may prove valuable in approaching the problem of gravimorphogenesis:
- protoplasts from higher plants, which can deposit new cellulose cell walls, divide, multiply, undergo organised development and ultimately give rise to embryos and mature plants
- free somatic cells from higher plants, which through division under sterile conditions in a nutrient medium may express morphogenic competence and form somatic embryos that develop into plants
- propagules with predetermined organs (root/shoots), or growing points developed to varying degrees.

Some of these systems, if not all, may well be adapted to the establishment of a gravitationally responsive unit. Whether higher plant cells in isolation respond to gravitational stimulus, or rather a certain degree of morphological complexity is required, is one of the questions that can be answered on a Space Station. It should also be possible to establish whether or not gravitational responsiveness varies with different degrees of organisation or stages of morphological complexity. Since the normal uptake mechanisms in higher plants are dependent on well-developed transport structures within the tissue, it is of interest to learn whether these structures develop from cell culture systems as well under microgravity conditions as they do on Earth. It is also yet to be established whether several consecutive 'generations' of plant cells in culture (protoplasts, somatic embryos, suspension cells) can differentiate to mature plants in space.

The use of plant-cell cultures may also produce spin-offs in space plant

biotechnology. The production of secondary metabolites of economic importance may be modified under microgravity.

Chronobiology

here is some evidence, both from clinostat studies and from the 1983 Spacelab-1 (STS-9) flight, that the *Neurospora crassa* experiment revealed a marked reduction in the amplitude and clarity of the conidiation rhythm in some samples after 6 d. However, the biological rhythm of simple algae cells in Biorack on Spacelab-D1 appeared to be totally undisturbed. These contradictory results merit further investigation.

One of the questions still to be answered is whether circadian rhythms in cells are ruled by an exogenous 'Zeitgeber', i.e. some extracellular time signal. The experiment in Biorack with the algae *Chlamydomonas* addressed this problem. Microgravity may influence certain time-dependent biological processes in the single cell. For instance, the cell cycle, i.e. the sequence of events between two cell divisions, ranges from 15 to 24 h for an animal cell, and between two and four days for plant cells, with a characteristic duration for each type of cell. Lymphocytes require 72 h of incubation after exposure to the mitogen Con A for maximum activation. Cells from rape seeds take three days for one division cycle. Since it is conceivable that certain dynamic cell functions, such as cytoplasmic streaming, are influenced by gravity, it is of primary importance to assess the effects of space on biological clocks.

At least two fundamental questions can be asked about circadian rhythms in a microgravity environment:

– What is the effect of eliminating 24 h signals from subtle environmental parameters such as the Earth's magnetic field?
– What is the effect of microgravity on the rhythms in unicellular and multicellular organisms?

The 1 g reference centrifuge in Biorack allows these two effects to be distinguished.

Most important of all is the fact that the fundamental mechanisms of the circadian oscillating system has not yet been determined in any organism. If it can be established that circadian rhythms persist in a space laboratory circling the Earth every 90 min, and that the period of the rhythm is not an exact multiple of 90 min (so as to rule out the hypothesis that there is frequency demultiplication), then the problem of the effect of microgravity on the basic mechanism can be investigated. Since the generation of the rhythms is likely to involve the intracellular compartmentalisation of metabolically active compounds, and thus membrane transport systems, gravity may well affect the rhythms if there is disruption of subcellular organisation.

Results of Biorack Experiments on Spacelab-D1

The first Biorack flight on the German Spacelab-D1 mission yielded very interesting scientific results, which in all probability will serve as a foundation for many further studies. The experiments performed with single cells will be discussed here. Preliminary reports on the complete set of experiments have been published in a special issue of *Naturwissenschaften*. A detailed report on Biorack and on the results of all experiments has been issued recently by ESA as Special Publication SP-1091.

Experiments with bacteria

Bacteria can be considered the simplest form of life on Earth; they are single cells

not much longer than one thousandth of a millimetre, and they perform a great variety of essential functions in nature, without which the life chain could not exist. Under favourable conditions, bacteria proliferate rather rapidly by repeated cell division. Application of antibiotics can stop these processes and even destroy the bacteria.

It was shown in two Biorack experiments that microgravity has a stimulating effect on the proliferation of bacteria (*E. coli* and *Bacillus subtilis*). A third experiment suggests that space conditions make bacteria (*E. coli*) more resistant to antibiotics. Not only are these results scientifically interesting, they also suggest that humans are at greater risk in space than on Earth, given that there may be larger populations of bacteria, which are, moreover, less sensitive to antibiotics. This consideration is even more important in the light of the results of two other Biorack experiments, to be discussed later, which indicate that the human defence mechanism is weakened in space.

In some bacteria, two complementary cells meet and establish a physical bridge through which the DNA molecules that carry all genetic information are exchanged. The process, known as 'conjugation', yields cells with so-called 'recombinant DNA'. In modern genetic engineering, recombinant DNA is produced by the artificial introduction of isolated genes into bacteria. Bacteria with recombinant DNA produce compounds that are coded by the introduced gene and harvested from the culture. In this way — to quote a classical example — insulin can be obtained from bacteria whose DNA has been recombined with the human gene for insulin. Clearly, this technique has enormous potential for commercial application. In one Biorack experiment, inconclusive results were obtained concerning the artificial introduction of isolated genes into bacteria (*E. coli*). However, it was shown that transfer of DNA from one bacterium to another in the conjugation process is three to four times more extensive in microgravity than under 1 g conditions. This highly interesting result provides the first evidence of gravity effects at hitherto unexpected subcellular levels.

Some bacteria are able to overcome harsh environmental conditions, such as lack of nutrients, by changing into a dormant organism, the spore. This sporulation provides an excellent yet 'simple' model for the study of cell differentiation; the acquisition by the cell of different functions. In embryonic development, originally similar cells differentiate, for example, into skin cells and nerve cells that have totally different functions. A special case of differentiation occurs when a normal cell becomes a cancer cell and begins uncontrolled proliferation.

A number of Biorack experiments have addressed the question of differentiation. In the experiment with bacteria (*Bacillus subtilis*), the results suggest that sporulation is strongly retarded, if not inhibited, under space conditions.

To conclude with the bacteria experiments, it has been shown in Biorack that microgravity also affects the simplest and smallest forms of life. This result is not only important for the study on bacteria themselves, but has potential significance for the behaviour of all higher organisms in space, including man.

Experiments with unicellular organisms

Besides bacteria, there are many other organisms that also consist of a single cell. This cell is, however, of another, more complex type, the eukaryotic cell. In addition to having a distinct nucleus, the site of the molecules carrying the cell's genetic code, it contains many small bodies called 'organelles', with a variety of specialised functions. Such unicellular organisms occur in soil and ponds, and in vast numbers in our oceans (plankton), and are members of both the plant and animal kingdoms. They can vary in size from approximately ten times the size of a bacterium, to as much

as several centimetres in length, and they can perform a variety of functions reminiscent of those of true plants and animals. Moreover, like bacteria, these organisms can proliferate through repeated cell divisions, when sufficient nutrients are available.

Two Biorack experiments showed that, in line with the effect found on bacteria, microgravity strongly enhances cell proliferation in the algae *Chlamydomonas* and in the protozoan *Paramecium*. In *Paramecium* cell numbers four times higher than those obtained under 1 g conditions were found (Fig. 5.8). As mentioned above, the biological periodicity in *Chlamydomonas* appeared to be totally undisturbed under space conditions and thus, in this respect, the cells appear to function normally. However, they did undergo cell divisions at a faster rate.

A third experiment in this series studied the behaviour of a slime mold called *Physarum polycephalum* which, although it can grow to many centimetres in diameter, consists of one giant cell with millions of nuclei. An elaborate network of veins maintains a continuous flow of protoplasm, the direction of which reverses periodically. Also this experiment shows that normal periodicity was maintained. However, the velocity of protoplasmic streaming increased in microgravity. As with the other two experiments, this result may be interpreted as a speeding up of the processes of life at cellular level: normal internal rhythms are maintained, but proliferation rate is increased.

Experiments with human cells

Isolated single cells from human tissue such as organs, skin or blood, can be cultivated and studied in the same way as unicellular organisms. Two Biorack experiments have shown that microgravity completely inhibits lymphocyte activation, thus confirming the results obtained in Spacelab-1. The investigations were carried out on cultures of lymphocytes prepared on the ground and tested in space, and with whole-blood samples taken from the crew and tested in flight, respectively. In addition to the interest in the effect of microgravity on basic biological mechanisms, it also important to assess the health risk arising from an impairment of the efficiency of the immune system.

In conclusion, it is highly desirable that several, if not all, of the experiments mentioned be repeated in space. The biological importance of the outcome certainly justifies seeking the best statistics possible.

Figure 5.8. Population growth curves of in-flight and control cultures of Paramecium fixed at different times.

This chapter started with a simple review of biophysical effects and phenomena that differ under normal gravity conditions and in microgravity. They are, therefore, important to bear in mind when considering studies of cellular processes in space.

In some cases, the biophysical effects mentioned describe sensor functions, as in the case of 'balance organs' of plants and animals. In such cases, sedimentation of denser particles in individual — specially organised — cells provides the fundamental basis of the ability to recognise a reference direction. In most instances the reference direction is, obviously, that of the gravity vector. Evolution on Earth has certainly favoured organisms that are constructed to withstand and take advantage of the gravitational force.

It is worthwhile looking at an arbitrary cell system and discussing, with the above remarks in mind, the interaction between the cell components and gravity. Figure 5.9 shows a hypothetical unicellular organism, but the same considerations apply to a multicellular one also.
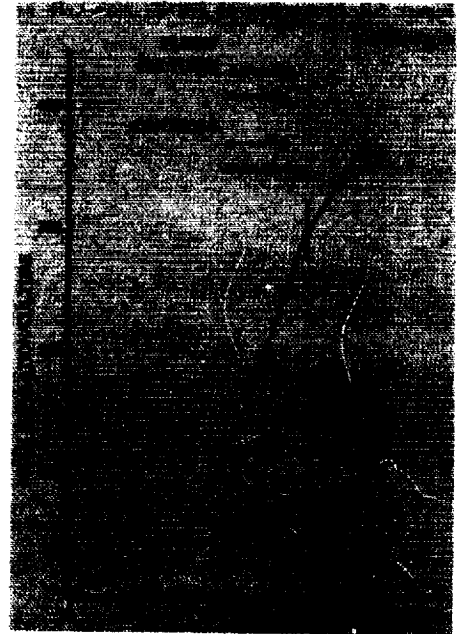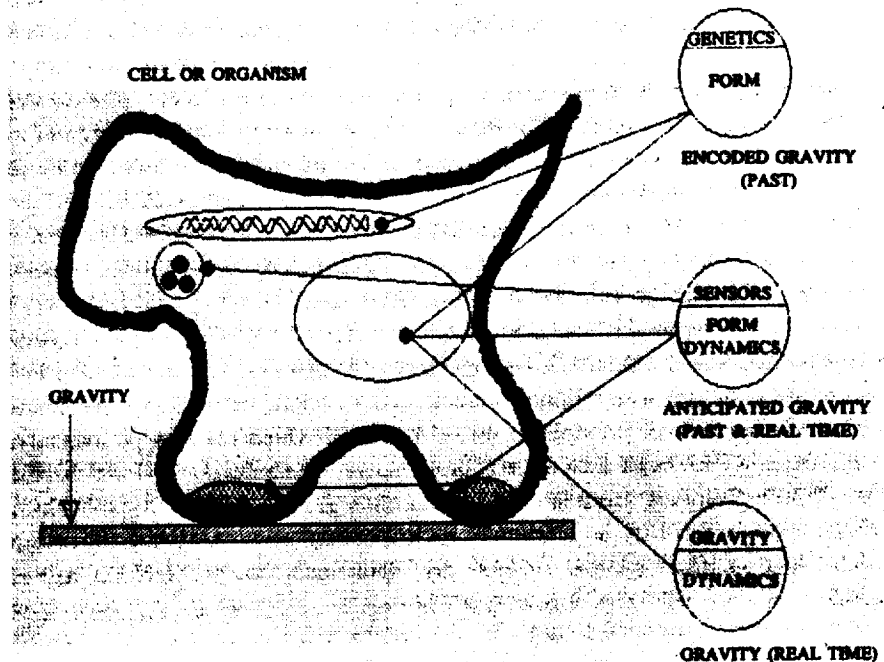
How Cells Could be Influenced by Gravity

Figure 5.9. Interaction of gravity with cells or organisms.

Gravity may act on at least three 'levels':
— through genes
— through sensors
— through molecular interactions.

Gravity acting through genes

During evolution, the ever-present force of Earth's gravity has been 'incorporated' into genes that determine the form and function of the organism. The basic form of plants and animals has been adapted to the environment the organism will be living in, and to the function it has to perform. In a sense, the three-dimensional morphology can be said to have been encoded in the genes through past interaction with gravity; it can be termed 'encoded gravity'. One would not expect this action of gravity to change over a few generations under microgravity conditions, since there is no reason to believe that the Darwinian theory of random mutations and selection would favour an acceleration of changes in encoded gravity. Thus, the basic form of a particular organism will, in all likelihood, be maintained even in a low-gravity environment.

However, expression of an organism's genom requires proper functioning of the appropriate biological machinery. If, for some reason, the machinery itself were inhibited by lack of real-time gravity, then expression would be impaired and no pre-established form could be generated.

Gravity acting through sensors

Sensors in this context are considered to be biological systems that provide real-time information about gravity. Information may be obtained directly from specialised structures, such as the vestibular organ in vertebrates or the statocytes in plant root caps.

It is important to point out that at the cellular level, the question of sensors is a rather complex one. If a living cell were to have a substructure with sedimentary heavy particles, that structure could be hypothesised to be a sensor organelle. However, the tension in structural cellular networks (e.g. the microfilament system) may itself somehow provide information to the cell about the gravity vector.

If the cell would really possess a gravity sensor organelle(s), then cellular network tension could well contribute to, or be mediative in, the act of sensing a changing gravity vector.

A similar remark can be made concerning gravity-mediated changes in energy requirements (also discussed earlier in this chapter). The energy spent by cells under 1 g conditions to maintain their positional homeostasis can be estimated. Changed levels of gravitation may change the cell's energy requirements and could hence provide information about gravity. It is argued that such a system could substitute for a real gravity-sensor organelle. As mentioned above, this is true in an integrated system that includes sedimentary particles giving positional information relative to the gravity vector.

Sensors generate the necessary feedback data to establish the precoded form of an organism successfully, to adapt the organism to changes in the environment and to maintain a proper balance. This can be called 'form dynamics'; they anticipate the force of gravity. Their very existence, however, is an expression of encoded gravity. Thus, anticipation of real-time gravity is performed by systems developed from past gravity environments.

It should be mentioned that both morphogenesis and sensor functions are dependent on appropriate biological machineries that, if themselves dependent on real-time gravity, may interfere with the system under study.

Gravity acting through molecular interactions

Past-time gravity information encoded in genes contributes to the form and function of an organism, while real-time gravity information obtained via biological sensors contributes to the form-dynamics of an organism. These contributions can only be made through complex biological systems, which ultimately are based on highly regulated molecular interactions. Interference with these interactions will obviously cause interference with the form dynamics discussed.

In earlier publications, a hypothesis has been described to explain gravity effects on cells. This hypothesis proposes that microgravity causes minute deviations in the cellular machinery which, due to a frequent occurrence in active cells, accumulate to produce measurable changes in the cell. Two possibilities for the occurrence of such small deviations were given: one assumes a change in the cellular structural network, and consequently a change in the cell's energy requirements; the other directly addresses the above-mentioned molecular interactions and their sensitivity to gravitational fields.

Systems that are thermodynamically far from equilibrium and non-linear, such as enzymatic reaction chains with positive or negative feedback, may show quite unexpected behaviours, depending on changes in relevant system parameters. For example, in such a system, an increase in the concentration of some chemical constituents to a certain threshold value may cause it to oscillate steadily in time and/or in space, or it may drive the system to a point where a choice can essentially be made between two different steady states. At such a point (a so-called 'bifurcation point'), the intrinsic choice is purely a matter of chance. However, the system becomes extremely sensitive to external forces, allowing it to enter one of two possible specific states. The point

has been made that relatively weak forces, like Earth's gravity, may have such pronounced effects on the subcellular systems as those discussed here.

The bifurcation phenomenon and its manifestation in biological cells would be of particular interest to gravitational biologists. It is tempting to speculate that in cells, particular molecular processes follow steady pathways that are determined by gravity. If so, microgravity could cause these processes to follow pathways beyond a presumed bifurcation point that are either 'normal', or different, driving the system into a different steady state, depending on the intrinsic choice made (Fig. 5.10).

In other words, a microgravity environment may cause some biological molecular interactions to go the 'wrong' way. Accumulations of such deviations may drive cells or multicellular systems into a non-functional state. Thus, it might be that biological systems apply the force of gravity so as to ensure that biologically meaningful pathways are followed.

Confirmation of such direct effects of gravity on the molecular interactions of biological systems would be an important scientific result in space biology.

Conclusions

Referring to Figure 5.9, we have discussed:

- past-time influences of gravity, which become encoded in genes and contribute to the form of an organism
- anticipated influences of gravity, which contribute via sensors to the form dynamics of an organism
- real-time influences of gravity, acting directly on the molecular interactions of the biological machinery.
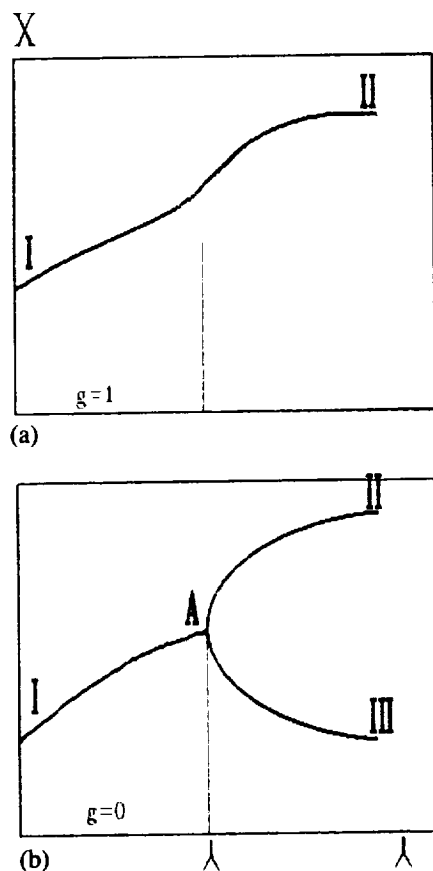

Figure 5.10. Biological pathways followed in response to the increase in a relevant system parameter (e.g. a growth factor, or a cofactor, or any other component specific to the system). Under normal gravity conditions (a) the pathway, which leads from I to II, has developed during evolution to a system which always functions correctly under Earth conditions. However, the system could appear to undergo bifurcation in the absence of gravity (b). Then a point A would exist at which the pathway, starting from I, can either lead to II or to III. III may not be meaningful to the biological system and the occurrence of it may drive the system into a non-functional state. (Ref. I. Prigogine & I Stengers, 1984)

The action of gravity via genes and sensors probably has much more relevance for multicellular organisms than for single cells. In other words, multicellular bodies are probably well suited to anticipating changes in the gravity vector. A distinction could be made between a particular effect of gravity on single cells being attributed to the action of sensors, or to direct action of gravity on molecular interactions (cell dynamics), by taking into account the presumed features of both actions, as shown in Table 5.2. The most important difference will be in the reaction time to changed gravitation and in the reversibility of the effect. Whereas sensor activity would show short reaction times and reversibility, action on cellular dynamic systems would be a relatively slow process yielding effects that may not be readily reversible.

In considering multicellular organisms, it is important to realise the contribution of single cells: (i) most organisms start their lives as a single cell, and (ii) most animals contain freely moving living cells (like white and red blood cells) as an essential part of their bodies. Thus, although cells in tissues of a multicellular organism are part of a high-level organisation that may prevent (or correct) malfunctioning of individual cells, free-moving or circulating cells are probably much less controllable. Direct action of gravity on the dynamics of these cells may therefore still influence the whole multicellular body.

It is important to point out that those effects of microgravity on cells that are based on processes like cellular network dynamics and energy transformation can also be revealed by the application of hypergravity. However, processes involving bifurcations can only be detected in microgravity. This basic fact supports the need for simultaneous investigations under microgravity, 1 g, as well as hypergravity.

Given the occurrence of bifurcations in far-from-equilibrium steady-state systems,

Table 5.2. Presumed differences in action of microgravity on cells if mediated via cellular dynamic systems or via sensor

	Cell Dynamics	Sensor Activity
Effect shown after:	Long exposure to microgravity	Short exposure to microgravity
Effect in:	Active cells only	Active and inactive cells
Effect:	Not readily reversible	Reversible
Result:	'Microgravity cell'	Normal cell sensing microgravity
Result:	Unpredictable behaviour	Programmed function

it therefore seems worthwhile adding a new field to space biology and studying the influence of microgravity on isolated, i.e. cell-free, biological processes. Some of these processes, e.g. assembly/disassembly of cytoskeletal proteins, when decoupled from the control of cellular machinery, might become more sensitive to a reduced-gravity environment. Moreover, many experiments designed to investigate this last aspect probably need only a few minutes of microgravity and, therefore, can be performed on a variety of spacecraft and rockets, e.g. sounding rockets.

Summary of Scientific Objectives

One of the most important objectives of cell-biology research in space will be identification of the cellular mechanisms sensitive to gravity, as discussed above.

There are also important biomedical questions to be answered: the culturing and analysis of blood cells from crew members may be useful for health monitoring, particularly during longer flights and aboard the Space Station. The development of inflight 'diagnostic technology' is therefore of primary importance for the manned space flights of the next decades.

Some of the findings concerning the adaptation of single cells to microgravity may yield important spin-offs for biotechnology. However, an extensive programme of basic research is required before the advantages of biotechnological applications can be assessed. To carry out such a programme, a space-qualified bioreactor, i.e. an apparatus for large-scale culturing of cells, with automated change-of-medium, pH and oxygen controls, and automated cell harvesting should be developed.

In summary, this chapter has essentially discussed three kinds of biological experiments in space that have high 'space relevance': basic cell research, biomedical diagnostics, and biotechnology. Together with other biological fields treated in this report, cell biology will certainly see important new information emerge as a result of space experiments in the decades to come.

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